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ORIGINAL ARTICLES

VIRAL HEPATITIS*

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I feel greatly honored in being asked to present the Gordon Wilson Lecture before this Association. Although I have not been familiar with all of the aims of the Association, I am aware that in creating a yearly lectureship which bears such a distinguished name, your major objective remains clearly defined: namely, the maintaining of a high level of clinical craftsmanship, a level not necessarily dependent upon the laboratory.

Almost a decade has now passed since the opportunity became available for the group at the Children's Hospital of Philadelphia to use volunteers who are still the basis for all work on viral hepatitis. It is almost a challenge to fate to mention that no deaths have occurred in the total group of volunteers who have helped us, well over 1500, but it would hardly seem necessary to mention that in this same decade a pediatrician can name a number of special reasons for being personally interested in geriatrics, growing older suddenly comes so often when dealing with severely ill volunteers. This review of certain features of viral hepatitis is necessarily in part a tribute to these hundreds of men and women, without whom there would have been little progress.

I should like to outline certain findings in viral hepatitis obtained primarily from clinical observation, which

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may well prove to have significance in several fields of investigation, beyond the study of hepatitis alone.

First, however, before one may consider application of knowledge in this field to other areas of medicine, it is necessary to establish more clearly a point of view concerning the nature of viral hepatitis itself, namely, as to whether it is one or more disease entities.

It is not necessary to consider serum hepatitis, or viral hepatitis B,* as a new disease entity. During our early experience over a number of years with viral hepatitis, it was rare that the attending physician thought of relating jaundice to the use of a needle or to a parenteral injection occurring months previously. The possibility of a 2 to 4 months' incubation period had been completely overlooked in the past in the same manner that the possibility of rubella in the first trimester of pregnancy causing cataracts in newborns had been overlooked, and there was far less excuse for the latter because rubella is a distinct disease entity, while jaundice has many causes, including epidemic hepatitis. Certainly as injections for diabetes and syphilis increased from 1920 to 1930, an infectious cause for jaundice related to the injections was suspected. It was when transfusions, large pools of plasma, and vaccines buffered with blood products came into broad usage that hepatitis B became a more obvious entity, and certainly a far more frequent one.

Often the belief that there are antigenic differences in the etiologic agents of viral hepatitis depends not so much upon the facts but rather upon the minds which receive the facts. Just as attitudes in politics depend often far more upon geographical location of the voters, meaning essentially the family background, so also background and position in a school of medicine deeply influence the avenues of investigation and the acceptance of data, even though similar data may be obtained by a number of investigators in more than one institution.

Also, by exciting so much interest and controversy, and by covering so many departments in medical schools, the liver has collected over recent decades a far more impressive family background, resulting in many firm beliefs.

For example, viral diseases of the central nervous system, in particular the viral encephalitides, in many instances have clinical and histological pictures which in general are indistinguishable from each other, and yet little question is raised by the pathologists or internists when viral cross-immunity studies or neutralization studies show that they are completely different etiologically; it is left to the virologists to decide. They decide they are different and the decisions stand.

Similarly, epidemic influenza A and B are indistinguishable in incubation periods, in clinical picture, and histologically, but here again the original demonstrations of lack of cross-immunity or cross-neutralization by the virologists is accepted. Not so viral hepatitis. Viruses may be considered as relative newcomers to the pedigreed liver family, during the inevitable up-

* The use of the letters A and B in viral hepatitis was initiated in England to designate respectively infectious (epidemic) hepatitis (IH) and serum hepatitis (SH) and the letters A and B were also adopted by the World Health Organization. Although viral hepatitis under field conditions, broadly speaking, would fall into these two categories, A and B, key studies on cross immunity and other factors have been carried out with only a few viral strains. While these studies also support to an extent the separation into these two categories, until serologic tests are available there is no certain means of determining the accuracy of classification into A and B. Despite these difficulties the studies, as indicated here, point clearly to certain antigenic differences in the virus strains.

heavals affecting medicine in wartime.

In viral hepatitis, as in the encephalitides and in epidemic influenza, the clinical and histological pictures of epidemic hepatitis and serum hepatitis are essentially indistinguishable.

However, a well demonstrated lack of cross-immunity both under epidemic conditions and experimentally in volunteers[12,17,20] of what have been termed virus IH or A, and virus SH or B (the letters A and B are simpler and more acceptable); these proven facts still appear to be unacceptable to a considerable number of internists, pathologists, and those interested in certain metabolic functions of the liver.

To an extent such doubts may be the result of the limited number of volunteers available for cross-immunity studies under experimental conditions, but such limitations were not present in studies of the disease under natural conditions such as obtained in North Africa in the studies by Gauld[7]. In these studies not only was there no immunity to epidemic hepatitis as a result of previous attacks of serum hepatitis (yellow fever vaccine jaundice) but actually the previous serum hepatitis had produced an increased susceptibility to the epidemic disease.

Havens carried out cross-immunity studies between A and B in one direction, while at the same time in Philadelphia we carried out reciprocal cross-immunity studies, namely, starting first with A and later testing the volunteer's resistance with B and vice versa. The fact that the two groups of workers obtained a strikingly similar lack of cross-immunity between A and B is all the more important because the subject at test was man himself.

It may appear that this is belaboring a point of view already well established. It would not appear to be so when as well-known a worker as Sir John McNee, in his recent Harveian Lecture[15], strongly advocated the view that these viral agents were antigenically the same. This point of view appears to be more readily accepted by those who have worked for many years in the numerous metabolic or pathologic aspects of liver disease and thus may look upon the more recent viral studies with jaundiced eyes. In fact, the jaundiced eye is often quite evident in liver disease.

Although lack of cross-immunity appears to be the most important criterion for distinguishing the viral encephalitides and the epidemic influenzas, one from the other, the viruses of hepatitis have intriguing differences in addition to lack of cross-immunity.

The gamma globulin fraction from the Red Cross pools of plasma has been highly successful in stopping epidemics of hepatitis[25] throughout the country as well as abroad, whether used in controlled or uncontrolled studies, and recently in doses as little as .01 cc. per pound body weight[23]. Most of these studies have been conducted by our own group of workers, but a sufficient number of corroborative studies have come from all parts of the country to overcome whatever jaundiced mote there may be in our own eyes. After all, studying jaundice so closely we cannot always be sure of having cast the jaundiced beam out of our own eyes in order to see clearly to cast out the motes elesewhere. In contrast to the epidemic disease, Red Cross gamma globulin in serum hepatitis, with a single known exception[9], has not prevented the disease under natural conditions or in volunteers; nor has it neutralized the virus B[22], even though recently in such studies with Dr. Drake *et al.*[4] we have used gamma globulin, collected from volunteers, convalescent 4 months to 6 years from jaundice caused by the Ft. Bragg strain of virus, and fractionated by Sharp & Dohme

Company for this particular purpose. It is still possible that the neutralizing antibodies are in another fraction of the globulin than the gamma fraction, or they may rise and fall during the first 3 months of convalescence. However, a previous neutralization test with convalescent plasma (2 cc. of infective serum mixed with 10 cc. of convalescent plasma)[22] did not suggest that antibodies were present. The same convalescent plasma was also injected in 20 cc. amounts at 3 successive periods after parenteral inoculation of the mixture of infective plasma and convalescent plasma without evidence of protection.

Another constant difference is the presence of virus of the epidemic disease in the stools, with consequent ease of cross-infection by contact or by the milk, food, or water-borne routes. We have been unable to produce serum hepatitis even by parenteral injections of filtrates of stools from such cases obtained during the early disease period, and the general lack of epidemics starting from hepatitis B is obvious. The types of influenza do not have nor appear to need substantiation of their separation by such characteristics.

The incubation periods of viral hepatitis A and B on occasion are similar and with the same strain of virus A there may be prolongation of the incubation period to the length seen in some cases of B; but if one calculates the mean incubation periods of both diseases in large numbers of volunteers and in field epidemics, A will average 20 to 30 days, while B will average 60 to 90 days. When the incubation periods are longer, in many instances of both A and B, our experience also strongly suggests that the infecting dose contained fewer viral bodies, namely, was of low titer, or was attenuated in some way, even though individual variation in resistance must play an important part.

This is well illustrated in our studies on A in 3 instances, (1) when contaminated water from a summer camp had stood at room temperature for a considerable period before being ingested by volunteers (about a 60-day incubation period)[18], (2) when artificially infected water was treated by flocculation and filtration, resulting in a marked increase in the incubation periods of the control volunteers receiving the untreated water (a 30 to 40-day incubation from the treated water, and a 20 to 25-day incubation in the controls)[19], and finally (3) when a single individual had ingested water from a well which had apparently been contaminated a considerable time previously and in which case a large part of the contaminated water must have been used and the remaining portion considerably diluted before he ingested it (a 56-day incubation period)[6]. Ingestion of contaminated food or direct contact were also possible, though less probable, sources of infection in this case.

Although the last individual may have had a chance infection from some other source, the origin seemed fairly clear because he was the only one in his rural area who had the disease at that time and when and where he was infected could apparently be localized to a single day and place. The reciprocal relation of number of viral particles to the length of the incubation period in virus B or its attenuation is also suggested by the results both our group and Dr. Roderick Murray's[16] group have been obtaining in studies on an artificially infected pool of plasma originally prepared by the late John Oliphant and containing the Ft. Bragg strain of virus B from our laboratories. This pool, which was shown by Dr. Murray to have a titer of at least 10^{-4} not only produced longer incubation periods in its higher, than its lower, dilutions, but when irradiated

by apparatus which apparently had been effective in sterilizing commercial pooled plasma with possibly less virus, again produced longer incubation periods than in the control volunteers who received the unirradiated plasma. For instance, this infected pool irradiated on a cylinder type of apparatus used by Sharp & Dohme produced hepatitis with jaundice in only one of our 6 volunteers injected parenterally, the one case having an incubation period of 108 days. Experience of Dr. Murray's group[16] with this material covering 43 subjects, who developed hepatitis shows that while the mean incubation period of those subjects who received untreated plasma was 84 days; that for those who received plasma which had been treated in some manner (such as by ultraviolet irradiation, heating or extreme dilution) was 99 days.

I have outlined at some length the factors which appear to have changed the length of incubation of viruses A and B, since in particular the lengthening of the incubation period of virus A up to 40 to 55 days has been considered by some as suggesting the identity of the two viruses. If such factors have already been shown to alter the incubation periods both under natural and experimental conditions with virus strains known to produce no cross-immunity, the attempt to unify these two agents, under a single antigenic type, on the primary basis of incubation periods appears clearly to be based on attitude and not on facts. It would be as sensible to unify influenza A and B antigenically because they have the same incubation period, while in viral hepatitis A and B the mean incubation periods as mentioned above of the vast majority of cases are farther separated than almost any other two infectious diseases now known.

A fifth difference which accords well with the above evidence concerning gamma globulin is the common tendency for a high incidence of B to occur in later life, while epidemics of A rarely strike older individuals when they sweep through a community. In hepatitis A this immunity appears usually to be permanent and adds its antibodies when collected to the general pools of plasma for fractionation, while virus B either is a relatively infrequent cause of disease or does not produce a very solid immunity. In the original studies on homologous immunity with Neefe[17], the test of resistance by using the same virus parenterally in volunteers who had had jaundice from the Ft. Bragg strain previously, resulted in questionable hepatitis in at least 5 of 9 men.

It seems appropriate to add to the above 5 differences 2 others which are not as clear-cut and which still require an amount of study that already promises to be highly fruitful.

The carrier state, although well recognized for a number of years in hepatitis virus B with respect to the blood, has only recently been studied in volunteers. Nothing is known concerning the presence or absence of a blood-borne carrier state in hepatitis A, although this virus has been found in the stools of 2 children chronically ill with mild hepatitis without jaundice for 5 and 15 months respectively, in an endemic infection in a Chicago orphanage studied together with Capps, Bennett, Drake, Ettinger, and Mills[1]. Apparently the carrier state in hepatitis virus B, if one accepts the long incubation period as a general indication of the presence of this virus, has been found in at least 7 individuals, all with no history of jaundice. Since the carriers of hepatitis virus B were discovered chiefly by the resultant jaundice in recipients of their blood, and since individuals who have a history of jaundice are usually rejected as donors, it is not strange that most

of the carriers thus far detected gave no history of the disease. Several of the carriers have had chronic hepatitis as shown both by biopsy and by positive liver function tests[2,3,14]. At least 2 have been chronic alcoholics, thus raising the question of a possible relation between hepatitis virus B and alcohol in the production of chronic fibrosis of the liver.

I am mentioning hepatitis virus B in relation to the carrier state because again there appears to be a distinctly higher incidence of the carriers of this virus than of carriers of hepatitis virus A, although this difference is based on as yet inadequate evidence, and could not be considered as an important distinguishing feature between the two viruses.

A final point of differentiation is of increasing importance as the data accumulate, namely, the use of a skin test developed chiefly by the Drs. Henle at The Children's Hospital of Philadelphia, which consists of irradiated amniotic fluid from embryonated eggs infected with hepatitis virus A[13]. The irradiated amniotic fluid is injected intradermally in doses of 0.1 cc. of undiluted fluid or diluted 1:10, with a control in the opposite forearm of irradiated non-infected amniotic fluid. Previous experience of the tested individual with virus A is generally indicated by a red and usually indurated reaction above 10 by 10 mm. in diameter at 24 hours. When the test material is adequate the accuracy of the test as conducted in several thousand individuals appears to be about 80 to 90%, a percentage approaching that of the Schick test[24]. The test material is not commercially available on account of its lack of stability, although lyophilization has aided considerably in this respect. There have also been many false positive tests in control materials and adequate material has been difficult to produce. Recently use of the lyophilized material in large outbreaks in various parts of the country has furnished valuable epidemiologic data to both our own group of workers and to a few others who have used the test in conjunction with our workers. One difficulty also lies in determining that all of the virus in the test material has been inactivated by irradiation, since studies with the test suggest that immunity to hepatitis A may be produced by the skin test itself[5].

Thus far the studies with the test serve our purpose here in distinguishing between viral hepatitis A and B in that individuals who have had the latter disease react positively to the test in the same percentage one would expect for a random sample of the population of the same age range and not at all in conformity with the tests in individuals who have had epidemic hepatitis. However, hepatitis B occurs so often in older individuals who already are likely to have had some experience with hepatitis A, that a considerable percentage of these individuals have positive tests.

If the test fulfills its early promise of high percentage of positivity in epidemics thus far studied[1], it again should aid in clearly separating the viruses A and B.

The necessity of limiting the studies to volunteers, since no other animal is susceptible, emphasizes the importance of developing serologic tests for both viral agents. Usually the skin test material when diluted 1:10 has no longer sufficient antigen to be active, thus indicating by its low titer the chief reason apparently for the lack of adequate serologic tests by the use of infected amniotic fluid. The accompanying Table 1 recapitulates the points above outlined.

I have outlined the differences in some detail because they review some of the more important recent findings in viral hepatitis and unless these find-

ings are thoroughly understood it is too easy to theorize about the antigenic unity of viral hepatitis. Most of the work to date and particularly in the last few years the skin test, as used in epidemics widely separated in time and space, suggest that hepatitis virus A may be a single antigenic entity similar to measles, to which one attack gives immunity, and for which antibodies remain in the blood during life in considerable quantities. On the other hand, the information is certainly incomplete concerning the unity or multiplicity of antigenic types in viral hepatitis B. Obviously there may be strain differences in both A and B which only the development of serologic tests could clarify.

The 7 differences outlined offer conclusive evidence that there is an antigenic distinction between hepatitis viruses A and B. That these are apparently greater than mere strain differences, such as those found among the strains of influenza A, appears quite probable, because of the lack of immunity and of serum antibodies in the older groups of the population to hepatitis virus B.

Andrewes[8] has recently described a viral hepatitis with jaundice of mice which apparently has no immunologic relation to the human viral hepatitis, but which includes two agents, the one being susceptible to aureomycin or terramycin, and the other resistant, the compound infection requiring both agents for its full activity in the liver. Only one of these is a virus, while the other is an organism, larger than a virus and endemic in mice, *Eperythrozoon coccoides.*

In human viral hepatitis, since the liver actually appears to be sensitized by hepatitis virus B, so that it is more susceptible to infection with virus A and vice versa, there may be a synergistic reaction between the two viruses.

TABLE 1.—CONTRAST BETWEEN VIRAL HEPATITIS A (IH) AND B (SH)

	A	*B*
Cross-immunity	0	0
Protection by gamma globulin*	+	?0
Virus in stools	+	0
Incubation (days)	20–30±	60–90±
Usual age range	Below 30 years	All ages
Blood carriers	?0	+
Skin test**	+	0

* From Red Cross pools of plasma by ethanol fractionation method.

** Chick embryo amniotic fluid infected with hepatitis virus A (Akiba strain) and irradiated with ultraviolet light. Still in the experimental stage.

No susceptibility to aureomycin, terramycin, or other antibiotics has been demonstrated. Certainly human viral hepatitis does not appear to be a compound infection of two viral agents A and B.

These considerations lead to an important point in chronic viral hepatitis which may have broad significance in other diseases. When we began to study the effect of aureomycin on both acute and chronic viral hepatitis A, it became apparent that a beneficial effect occurred in some of the chronic cases but not in the acute cases when moderate doses of this antibiotic were used. Theoretically this was originally explained by a possible sparing action of the aureomycin as a result of reduction in bacterial action in the intestine: in bacteria themselves, the

products of the bacteria, or the reduction in absorption of materials produced by bacteria as a result of their action on intestinal contents. This theoretical concept was first studied in viral hepatitis of man with Sborov and Shaffer at the Army Hepatic and Metabolic Center[21], Valley Forge Hospital, and later thoroughly with Gyorgy[11] in hepatic necrosis of rats on diets deficient in the sulfhydryl amino acids and vitamin E, with British yeast as the only source of protein.

A large proportion of rats are partially protected from such hepatic necrosis when fed aureomycin and penicillin. These results have been carried over by Gyorgy[10] to the study of hepatic cirrhosis of rats produced by choline deficient diets, and aureomycin in a similar manner has protected most of them from cirrhosis.

The results at present suggest an important area of interaction between intestinal bacteria and a damaged liver; whether damaged by viruses, deficient diet, or radiation injury (as indicated in radiation injury by Dr. Philip Miller and his group in Chicago[15a]). It is possible that the outbreaks of diarrhea so often preceding epidemic hepatitis may either spread the hepatitis virus from an early case or from an intestinal carrier, or by absorption of bacteria or their products through the liver may render it a more fertile soil for the later hepatitis virus. The interaction of intestinal viruses and bacteria is essentially an unexplored field. Our studies with aureomycin, terramycin, and penicillin afford one approach to this field. Infections of the respiratory tract illustrate one type of interaction between viruses and bacteria. It appears that compound infections which include the interaction of viruses and bacteria may occur in varied forms in the intestinal tract. The liver may well aid in the study of such compound infections because it represents, particularly in its left lobe, which in contrast to the right lobe absorbs more of the products of the large intestine, a sensitive filter for detection of viral or bacterial products or for the microorganisms themselves. As in hepatic necrosis of rats, altered livers may be used in animals as sensitive indicators of intestinal flora. Viral hepatitis of animals could well be used also for similar purposes.

The follow-up of cases of chronic viral hepatitis and of carriers would strongly suggest that chronic fibrosis of the liver is far more closely related to these viruses than has previously been realized. The possible compounding of such factors as chronic amebic infections, carriers of such organisms as *S. typhosa* or *S. cholerae suis*, virus carriers or chronic cases of viral hepatitis, alcoholism and nutritional deficiencies, and chronic poisoning from various chemicals or metals must be considered. Since viral hepatitis, at least in its A form, strikes most individuals, its possible relation to such compound effects is particularly important. Does it remain in the liver at times as the virus of herpes simplex remains in the skin and is it excreted with the bile into the intestine? Does it remain in the intestinal tract mucosa in the same manner and cause digestive disturbances which are reflected in the liver by direct extension or by absorption products? If continuously a hazard, does it interact in the liver with bacteria or their products over a period of years?

Although it has been only a decade, as mentioned, since the viruses of hepatitis have been actively investigated, and in only a few places because of the requirement of volunteers, we have means at least of controlling completely sharp outbreaks of epidemic hepatitis, and the complete control of the hepatitis virus (or viruses) B in plasma at

least appears imminent. When one compares such progress in the practical field of control with the progress in such a viral disease as poliomyelitis, which has been now studied more widely with a number of species of animals other than man, for at least 4 decades, the advances in knowledge of viral hepatitis appear to be relatively rapid. There is at present the greatest hope that the volunteer may be replaced by the chick embryo, by tissue cultures, or by some other susceptible animal, so that even more rapid progress may be made without the attendant risks.

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BELL'S PALSY TREATED WITH CORTISONE

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THERE have been many treatments for Bell's palsy. All have been non-specific, tending to treat the effects rather than the cause, and no treatment has been able to achieve a dramatic remission in the facial paralysis. Recovery, when seen, is usually slow. The greater number of cases treated with accepted physiotherapeutic methods show improvement only after several weeks. Moreover, the longer the duration of the acute stage before improvement begins, the more common is residual paralysis. Although the onset has often been related to exposure to cold and inclement weather, and is often associated with respiratory infections, no specific etiology has been proven.

The changes which occur in the nerve and its sheath have been carefully studied, and it has been found that both are involved in an acute inflammatory reaction. It has been shown that edema of the nerve sheath as it passes through the dense bony portion of the fallopian aqueduct between the horizontal canal of the labyrinth and the stylomastoid foramen so compresses the nerve fibers as to interfere with their normal function. Morris[2] reported several cases in which the bony portion of the horizontal canal was laid open to relieve this acute nerve compression and the sheath cut at this point, leading to prompt restoration of nerve function. Hall[1] described the lesion in cases of Bell's palsy found at operation for decompression of the facial nerve. In all instances an acute inflammatory reaction of the nerve was found with an exudate in the cells at the tip of the mastoid process, The bone near the stylomastoid foramen was found to be soft and the facial nerve very edematous.

Since the inflammatory reaction was of a non-specific nature, and since cortisone has been successful in relieving certain non-specific congestive changes, it seemed logical to apply its action to this type of case. Accordingly, one such case of Bell's palsy was treated with cortisone with very prompt and complete recovery. This case was reported in October 1951[4], and the hope was voiced that others would be encouraged to use this treatment. Since then 5 additional cases of Bell's palsy have been treated in this manner by the writer, and the results have been sufficiently gratifying to prompt this further report. The original and 6 additional cases are herein presented.

Case Reports. CASE 1. A female patient, aged 59, was admitted to the hospital with a left facial paralysis which was first noted on arising that morning. She had previously had an upper respiratory infection for several days. She showed complete flaccidity of all left facial muscles. The left lower lid was completely everted and marked lacrimation was evident. The left corner of the mouth showed considerable drooping with drooling of all fluids taken. The following day the patient was given 100 mg. of cortisone intramuscularly every 6 hours. Forty-eight hours later the patient volunteered the information that she was regaining control of her facial muscles. She showed less lacrimation and less drooling. The following day there was definite further improvement, and with return of control of the lower lid no lacrimation was evident. The left corner of the mouth was definitely under voluntary control. On the 5th and 6th days the dosage of cortisone was decreased to 100 mg. every 8 hours. Improvement was noted daily and on the 7th day muscular control was completely re-

covered. Over the next 6 days the dosage of cortisone was gradually decreased. The patient was discharged on the 13th day with no evidence of residual paralysis.

CASE 2. A young girl, aged 13, was admitted to the hospital with paralysis of the left side of her face and loss of taste over the left side of the tongue. She had first noted weakness of the face 3 days prior to admission. This had increased in severity until she was unable to retain liquids in her mouth. There was complete loss of function of the left eyelid, inability to wrinkle the left forehead or raise the left corner of the mouth. The remainder of the examination was noncontributory except for a temperature of 100.2° F. She was started on 100 mg. of cortisone intramuscularly every 6 hours. After 24 hours of therapy, she volunteered the information that her taste had returned. This was confirmed by appropriate tests. The dose was reduced to 50 mg. every 6 hours for the second day. On the 3rd day of therapy the first signs of improvement were noted. Drooling of liquids stopped and she was able to demonstrate some closure of the left eyelid and with concentrated effort, the ability to raise the left eyebrow. The dosage was decreased to 50 mg. every 8 hours on the 4th day. Further improvement was noted on the 7th day, when there was a dramatic change overnight. She regained good function of the left eyebrow, left eyelid and all left facial function. Recovery of all facial function was complete on the 10th day. Over the following 3 days the dosage of cortisone was slowly decreased to avoid abrupt termination of the drug.

CASE 3. A female, age 25, was admitted to the hospital with loss of motion of the muscles of the right side of her face. She stated that 5 days prior to admission she had experienced pain over the right mastoid region, associated at the same time with inability to retain fluids which drooled out of the right corner of her mouth. She had also lost taste over the right side of her tongue. This loss of facial function increased in severity until on admission there was inability to close the right eyelid, elevate the right eyebrow, wrinkle the right forehead, or control the right side of the mouth. She was started on cortisone, 100 mg. every 4 hours for the first 24 hours, and 100 mg. every 6 hours for the second and third days. On the second day of treatment she showed slight ability to close the right eyelid with concentrated effort. She also volunteered the information that she had a sensation of feeling again in the right side of her face and lips. On the third day there was improvement in taste over the right side of her tongue, and she could initiate easy motion in the right lower lid. On the 4th day the dosage was decreased to 100 mg. every 8 hours. The course continued without any noticeable change through the 7th day. The dosage was further decreased on the 8th day to 100 mg. every 12 hours, and on the 9th day dramatic improvement was observed. She regained control of her mouth, could wrinkle her forehead, and was able to close her eyelids with ease. The dosage was decreased to 50 mg. every 12 hours and gradually decreased to elimination over the next few days. During these last few days recovery proceeded daily at a rapid pace. All facial function was recovered completely and the only residual difficultly was slight loss of taste remaining in the anterior third of the right side of her tongue.

CASE 4. A 65-year old male was seen with a left facial paralysis. This had begun 5 days prior to the onset of treatment with pain in the left ear. The peripheral facial paralysis was complete with loss of motion in the lower lid, continuous lacrimation, and drooping of the left corner of the mouth. Treatment consisted in the administration of oral cortisone, 100 mg. every 8 hours for 3 days, and 50 mg. every 8 hours for the next 4 days. Marked improvement was noted on the third day and complete recovery after 7 days.

CASE 5. A 45-year old female was first seen 9 days after the onset of a peripheral facial palsy on the right side. This was quite severe and was accompanied by loss of taste over the anterior two-thirds of her tongue on the right side. She was given 500 mg. of cortisone orally in the first 24 hours, after which her taste returned and she was able to close her right eye. On the second day she received 400 mg. of cortisone and for the following 3 days, 300 mg. daily. Facial muscle function began to return on the 8th day at which time, the dosage had been decreased to 200 mg. daily. Function continued to improve rapidly and was completely normal on the 12th day when all medication was stopped.

CASE 6. A 35-year old male patient presented himself. He displayed evidence of paralysis of the right side of his jaw. Five days previously on awakening, he found that he was unable to use the muscles of the right side of his face. There was marked eversion of the lower lid with lacrimation, complete loss of control of the right side of the mouth, drooling of fluids, and inability to wrinkle the forehead on that side. He also

complained of a roaring noise in the right ear.

He was started on cortisone tablets, 75 mg. every 6 hours for the first 24 hours and 50 mg. every 6 hours for the following 6 days. No change was noted until the 5th day, when the patient was able partially to close the right eye and elevate the right eyebrow. On the 7th day there was a marked improvement both subjectively and objectively. The patient stated that he felt better control of the muscles of his forehead. He was able to close his right eye, use his lips with effectiveness, and to wrinkle his forehead.

then had shown no evidence of improvement. The paralysis was noted to be severe with involvement of all muscles on the affected side. She showed no nerve response to faradic stimulation. She was started on 400 mg. of cortisone daily by mouth and continued on large dosage with no response after 14 days on medication. Observed 14 days later, about 38 days after the onset, there was still no sign of recovery.

Comment. Doubt can be raised as to the efficacy of cortisone in a condition which often shows spontaneous

TABLE 1.—DOSAGE SCHEDULE IN MILLIGRAMS OF CORTISONE GIVEN TO 7 PATIENTS WITH BELL'S PALSY

		Case No.						
		1	*2*	*3*	*4*	*5*	*6*	*7*
Day of Treatment	*1*	400	400	600	300	500	300	400
	2	400	200	400	300	400	200	400
	3	400	200	400	300	300	200	400
	4	400	150	300	150	300	200	300
	5	300	150	300	150	300	200	300
	6	300	150	300	150	200	200	200
	7	200	150	300	150	200	200	200
	8	100	100	200	100	200	150	200
	9	75	50	100	75	100	150	150
	10	50	25	50	50	50	100	150
	11	25		25	25	25	100	50
	12	25		25		25	100	50
	13						50	25
	14						25	25

The dose of cortisone was decreased to 50 mg. every 8 hours for the 8th and 9th days, then further decreased to 50 mg. every 12 hours for the 10th, 11th, and 12th days. His recovery was quite complete by this time, and for the next 4 days the dose was slowly tapered off so as not to stop medication abruptly.

CASE 7. A 21-year old female was seen with the peripheral type of paralysis of the right side of her face. The paralysis was first noted 10 days prior to admission and since

improvement. However, it should be pointed out that in the average mild untreated case of Bell's Palsy, recovery is not evident until after 4 to 6 weeks. Patients who do not improve by this time commonly show evidence of residual nerve atrophy and paralysis. In 6 of our seven cases the recovery began within the first week of therapy and was complete by the end of the second

week. This uniform response could hardly be attributed to spontaneous recovery.

The beneficial action of cortisone in these patients can be assumed to be due to a reduction in the congestion and related ischemia of the nerve and its sheath in the bony canal. It follows, therefore, that the cases which could best benefit from this form of therapy would be those in which treatment can be begun soon after the onset, since prolonged edema of the nerve and its sheath could result in irreversible nerve atrophy. The longest time which elapsed between the onset of symptoms and the beginning of treatment in the successful cases was 9 days. The seventh case received cortisone only after a severe paralysis had been present for 10 days, during which time nerve atrophy as indicated by faradic test, had taken place. This is not intended to imply that all cases will show nerve atrophy after 10 days, since the degree of atrophy is also dependent upon the severity of the inflammation. However, it should be emphasized that this is not intended as a treatment of old cases of Bell's palsy.

It was felt that whatever advantage could be derived from the action of cortisone should be attained as quickly as possible. To produce the maximum effect promptly large doses of cortisone were employed initially. Table 1 shows the schedule of dosage employed in these seven cases. Although the first cases were treated with intramuscular cortisone, the last 4 received cortisone tablets orally.

Summary. Seven cases are presented showing the favorable response of acute Bell's palsy to treatment with cortisone in 6 cases and failure in one. The rationale is assumed to be the ability of cortisone to relieve the acute edema and inflammatory reaction of the facial nerve and its sheath, which cause marked compression of the nerve as it passes through the bony portion of the fallopian aqueduct. This allows for early restoration of nerve function. Where nerve atrophy has already taken place, cortisone cannot be expected to have a beneficial effect.

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BODY POSITION IN RELATION TO VENOUS AIR EMBOLISM AND THE ASSOCIATED CARDIOVASCULAR-RESPIRATORY CHANGES*

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VENOUS air embolism is not a common accident in medicine. However, it is undoubtedly more frequent in occurrence than has been generally appreciated[20], and when it does occur, it is often fatal. The importance of the subject warrants a better understanding of the associated pathophysiology than is presently available. Except for electrocardiographic deviation[8,9,10,26], circulatory responses to air embolism have been studied in the experimental animal only a few times[8,12,13,31]. Data relative to changes taking place in respiration are equally infrequent. It is possible that a better understanding of these alterations would allow the development of more successful preventive and therapeutic measures.

Previous investigation led the authors to recommend the left lateral position as a means of treating venous air embolism[8,24,25], and it was suggested that the benefit obtained from this position was the result of displacement of an obstructing air trap from the right ventricular outflow tract. Such an air trap would be located in this portion of the lesser circulatory system when the animal was on the back or on the right side since, in these positions, it is the most superiorly located portion of the heart and the principle of air buoyancy must apply, of course. In the left lateral position the right ventricular outflow tract is located inferiorly to the body of the right ventricle itself and the air trap would be thus displaced into a larger space with less tendency to cause obstruction. It has been since pointed out by Wiggers[31] that such an explanation might be interpreted to imply a drop in pulmonary arterial pressure distal to the air trap located in the pulmonary conus region, and that this pressure, on the contrary, actually rises rather than falls[12,13,31].

This study was undertaken in an attempt to solve this enigma, and, at the same time, add to our knowledge of circulatory and respiratory adjustments that determine whether or not survival is to occur with varying doses of air and in various body positions. The opportunity was also taken to check the site of lodgment of the injected air in different positions of the circulatory system by necropsy following the completions of the various experiments.

Methods. Ninety-eight mongrel dogs were used. These were anesthetized with pentothal sodium (20 mg./kg.) and barbital sodium

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(150 mg./kg.) intravenously. Blood pressures were recorded by Statham strain gauges connected to catheters suitably placed with fluoroscopic guidance in a carotid artery, pulmonary artery, pulmonary vein or jugular vein in various combinations. The output of these gauges was led to Consolidated galvanometers. Light beams reflected from the mirrors of the latter inscribed on the moving bromide paper of an 18-inch-wide Waters-Conley camera. In every case the pressures that were later measured were end diastolic pressures. In many instances the pulmonary pressures were integrated against pleural pressures by means of a differential Statham strain gauge. Respiration was registered by means of a spirometer writing on a kymograph. The animals were lightly heparinized in order to prevent clots in catheters. Air injections were made into a cannulated femoral vein. Oxygen and carbon dioxide concentrations were determined from femoral arterial whole blood specimens. Hematocrit determinations were done in almost every case.

Electrocardiographic recording (usually V_R) was made on the same bromide paper as the other optical records.

Dogs were studied in various positions: on back, not turned after air embolism; on back, turned on left side after air embolism; on the left side during air embolism; and on the right side during air embolism. Varying doses of air were injected. The doses used were those which we found to approximate the fatal level in a significant percentage of cases. Injections of air were made as rapidly as possible, usually within 1 to 5 seconds.

All dogs were examined by autopsy at the close of each experiment to determine the presence or absence of air in the heart and lungs. The site of any residual air was carefully noted. Necropsies were carried out in the position (right lateral, supine, left lateral) in which the animals were placed at the time air was injected.

A biplane steroscopic angiocardiograph[4,5] (using 2 Fairchild magazines with 2 Roentgen-ray beams at right angles to each other, so that AP and lateral views are made simultaneously) was used to study, at frequent intervals, the air as it entered the heart and pulmonary vessels.

Results. A. EFFECT OF DIFFERENT BODY POSITIONS UPON SURVIVAL AFTER VENOUS AIR EMBOLISM. The post-injection survival rates in the supine, right lateral (right side down) and left lateral (left side down) positions, are summarized in Table 1. Also included is a group in which the injection of air was made with the animal in the supine position, but in which it was turned onto the left side 30 to 60 seconds after the first objective signs of air embolism (transient hyperpnea, progressive polypnea or the onset of apnea) had become evident. For the purposes of this paper polypnea is defined as an increased rate with decreased depth of respiration, and hyperpnea as an increase in both rate and depth. For purposes of statistical comparison, the group (No. 5) which received 7.5 cc./kg. in the supine position without

TABLE 1.—EFFECTS OF POSITION ON SURVIVAL FOLLOWING VENOUS AIR EMBOLISM

Group	*Cases*	*Died*	*Survived*	*Level of Confidence*[27]
1. Right side, not turned (7.5 cc./kg.)	9	9	0 (00.0%)	1%
2. Right side, not turned (5.0 cc./kg.)	18	14	4 (22.2%)	not significant*
3. Left side (7.5 cc./kg.)	16	6	10 (62.5%)	5%
4. On back, turned on left (7.5 cc./kg.)	18	7	11 (60.1%)	5%
5. On back, not turned (7.5 cc./kg.)	16	11	5 (31.2%)	control
6. On back, not turned (5 cc./kg.)	21	1	20 (95.2%)	1%

* If this category is compared with the series done on the back, not turned, receiving 5.0 cc./kg., then the level of confidence becomes 1%.

being turned was used as the control group.

It will be noted from the table that the survival rate in the control group was only 31.2%. When the dose of air in the same position was reduced to 5 cc./kg. almost all of the animals survived, giving a highly significant difference statistically between these 2 groups. A comparison of these with the 2 dosage groups (No. 1 and No. 2) in the right side position showed a highly significant difference between the controls and those receiving 7.5 cc./kg. (Group 1), since all of the latter died. The right side group receiving 5 cc./kg. (Group 2) had a small survival rate which was not significantly different from that of the controls, though the latter received 7.5 cc./kg. Thus the average lethal dose of air for dogs in the supine position is between 5.0 and 7.5 cc./kg., while for those in the right side position it is less than 5.0 cc./kg. The findings for the left side were much the same for groups 3 and 4, namely, for those that were initially placed on the left side and for those who were turned from the supine position onto the left side after air embolism. In each of these groups 7.5 cc./kg. of air was administered and the survival rate was approximately 60%. These rates constitute significant differences from the control group and demonstrate the advantage of the left lateral position in air embolism.

B. CIRCULATORY EFFECTS OF VENOUS AIR EMBOLISM. Immediately after the injection of air in all of the experimental groups, there was noted an abrupt fall in the systemic arterial pressure which often persisted for periods of 8 to 11 minutes. The fall in carotid pressure was associated with a bradycardia in the systemic arterial recording. This slowing of rate was in part actual, but in most instances it was due mainly to extrasystoles which developed intracardiac pressures sufficient to open the pulmonary, but not the aortic, valve. The pulmonary arterial end diastolic pressures rose abruptly immediately after the air injections in all of the animals, but then declined gradually to control values or lower. In those animals which recovered there was a secondary rise in this pressure, a phenomenon which was not noted in the majority of fatal cases in any of the groups. During this secondary rise in the surviving animals there was frequently noted the occurrence of an arrhythmia due to ventricular extrasystoles in bigeminal arrangement. It was often after this that an abrupt rise in systemic pressure occurred. In all of the animals there was an abrupt rise in the central systemic venous pressure. The pulmonary venous pressure was elevated soon after the injection of air in the majority of animals in which this was measured (5 out of 8 in Group 2, 6 out of 7 in Group 3, 3 out of 3 in Group 4), with the exception of Group 1, in which there was no rise in any of the animals.

The circulatory changes are of particular interest in the group of animals turned onto the left side after the induction of air embolism in the supine position. In 10 of these animals the pulmonary arterial pressure was recorded throughout the experiment. Six of these were in the surviving group and in all of these, following the usual primary rise and the subsequent fall in this pressure seen in all the other groups, there was a secondary rise following the turn onto the left side. Coincident with this secondary pressure rise, or immediately thereafter, there was a rise in the systemic arterial pressure, and there was also noted bigeminal rhythm. Of the 4 animals that succumbed despite the turning onto the left side, and in whom the pul-

monary arterial pressure was recorded, only 2 showed this secondary rise.

C. RESPIRATORY EFFECTS OF VENOUS AIR EMBOLISM. Disturbances in respiratory rhythm were dramatic features of all the experiments. In Group 1, immediately following the air injection, there was a brief period of polypnea followed by an equally brief period of hyperpnea, and then permanent apnea. It is important to note that in all of these animals, as well as in all those that succumbed in the other groups, the heart continued beating long after respiration had ceased. It should also be emphasized that in these, as well as in all other experiments, the respiratory effects preceded the onset of anoxia or hypocapnia. Terminally, hypercapnia was sometimes seen when anoxia had developed during a long period of apnea. In 3 animals injected with 7.5 cc./kg. when on the right side, bilateral vagotomy had been carried out before the experiment. The response of these animals to the injection was similar except that the terminal apnea was interrupted by a short bout of hyperpnea.

In Group 2, the 14 animals that succumbed demonstrated either polypnea or hyperpnea before fatal apnea supervened. In 3 instances a tendency was noted for the thorax to assume the inspiratory position during the polypnea preceding the agonal apnea. The 4 animals that recovered demonstrated initial hyperpnea or polypnea followed by apnea, and then a return of polypnea which continued to recovery. The latter followed the secondary rise of pulmonary arterial pressure to which we have already alluded.

In Group 3, polypnea was a consistent finding, and occurred with or without periods of apnea. When recovery took place this was via polypneic breathing.

In Group 4, polypnea was again noted in all the animals, having its onset 10 to 30 seconds after the air injection, and quickly followed by apnea. The subjects were turned onto their left sides either just before the polypnea terminated or just after the beginning of the apnea. In those which survived, recovery usually took place through a progressively decreasing polypnea toward control values with their slower and deeper respirations. The recovery period, however, might be interrupted by several periods of apnea, decreasing in duration, and separated by bouts of polypnea. Recovery was usually complete in approximately one-half hour. The onset of the polypnea which led to recovery was immediately preceded by the secondary rise in pulmonary artery pressure and the bigeminal rhythm referred to previously.

In Group 5, the respiratory disturbances were very similar. In the fatal cases polypnea was the initial finding, followed by fatal apnea. In the survivors recovery was by way of a secondary period of polypnea, pulmonary pressure rise and bigeminus.

In Group 6, the findings were the same as in Group 5, except that in 6 instances no apnea developed at any time. In these there was the usual initial polypnea with a progressive decline in amplitude, followed soon by a gradual increase, but remaining polypneic for at least 30 minutes.

In a special group of 16 dogs, not included in the Table 1 analysis, the effect of the introduction of small doses of air (1 cc./kg. or less) directly into the pulmonary arterial circulation was tested. A No. 8 catheter was introduced as far as possible into the terminal vessels of the lung and the air introduced at this point. There developed a persistent polypnea and hypotension without any change in heart

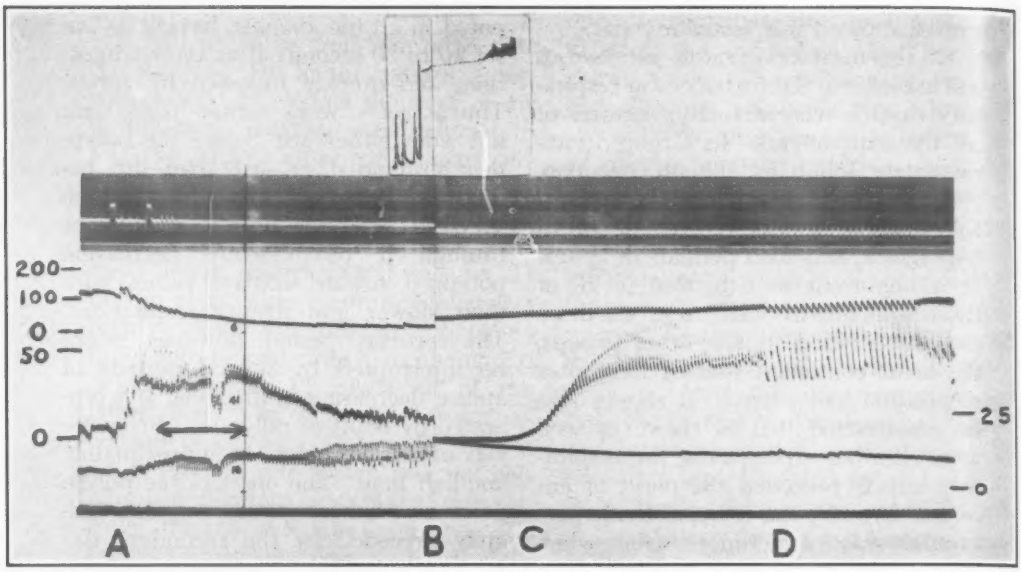

FIG. 1.—12-10-51. Dog on back, not turned, 7.5 cc. air/kg.; survived. Tracings from above downward: Electrocardiogram (V_R), aortic blood pressure, pulmonary blood pressure (integrated against intrapleural pressure), central venous pressure, respiration (pneumograph). Scales at left and right are in mm. of Hg, upper left scale for aortic pressure, lower left for pulmonary artery, right scale for central venous pressure. Double ended arrow represents 10 seconds. At A, air was injected (between two millivolt signals of electrocardiogram), at B 2.5 minutes are omitted, at C secondary rise in pulmonary arterial pressure during apnea, at D bigeminus, bradycardia, polypnea and persistent rise in pulmonary pressure, central venous pressure elevated. Small insert above electrocardiogram represents spirometer record for a period equal to entire figure but at a much slower speed (8:50). Line B is same for insert and main record. Respiration shows apnea and polypnea.

rate or electrocardiographic changes. In one instance a period of apnea preceded the polypnea. The amount of air introduced did not cause over-filling of the arteries with entry of air into the pulmonary conus. The respiratory and hypotensive effects were prevented by bilateral cervical vagotomy. In every instance, regardless of the dose of air or its situation in the pulmonary system, pulmonary artery end diastolic pressures were elevated. If air was introduced via catheters into the right atrium, right ventricle, or pulmonary conus, using doses up to 1 cc./kg., there developed polypnea with hypotension and bradycardia, and these effects were also prevented by vagotomy.

D. ROLE OF ARTIFICIAL RESPIRATION. Since our experiments indicated that respiration always stopped before circulation came to a halt after venous air embolism, further information on the role of respiration was needed. Five experiments were carried out to provide data on this point. Animals were placed on artificial respiration of a positive pressure type, and, after 15 minutes, air embolism was induced by femoral vein injection. Two dogs on their backs survived 7.5 cc./kg., but succumbed to a second dose of 10.0 cc./kg. one hour later. A third animal died from the first dose of 10.0 cc./kg. while on its back. Two other dogs placed in the left side down position

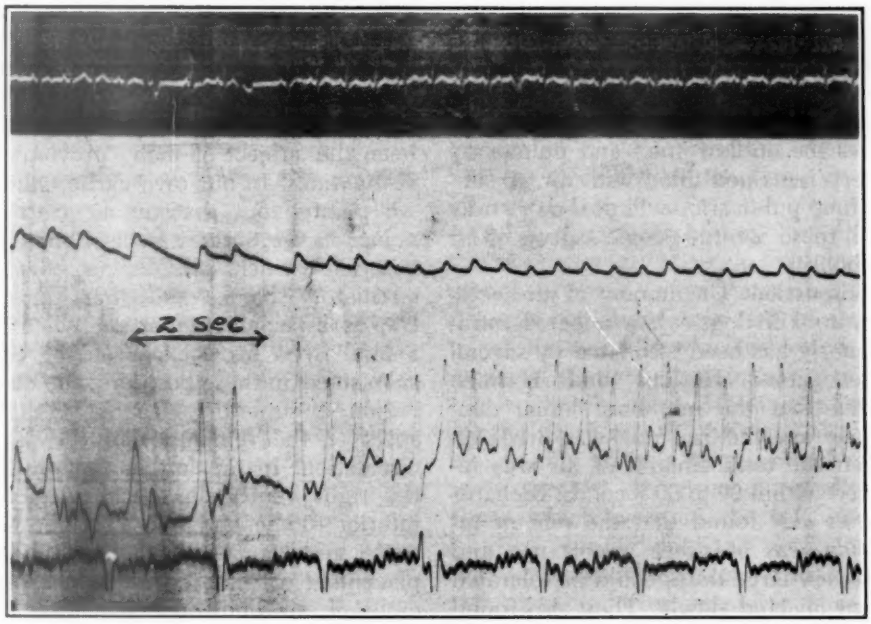

FIG. 2.—8-22-52. Dog on back. Tracings made at fast speed, double ended arrow indicates 2 seconds, during this period air was inpected (5 cc./kg.). Tracings from above downward: Electrocardiogram (Lead II), aortic blood pressure, pulmonary arterial blood pressure, respiration (pneumograph). There are more electrocardiographic complexes and more pulmonary pressure pulses than there are aortic pressure pulses during the abrupt fall in blood pressure. This produces the apparent bradycardia in the systemic pulse.

survived initial doses of 7.5 cc. and 10.0 cc./kg. respectively and one hour later were able to accept 10.0 cc. and 12.5 cc./kg. respectively without fatality.

E. ELECTROCARDIOGRAPHIC CHANGES. The electrocardiographic changes observed in these experiments were similar to those described in previous publications[8,9,10]. Lead V_R, the only lead studied in most cases, demonstrated diminution of the size of QS, and elevated T waves and ST-T junctions were common during the acute phases of air embolism. Extrasystoles were oriented with the beam moving downward.

F. DISTRIBUTION OF AIR AT POSTMORTEM EXAMINATION. In the fatal cases in all groups, air was found in the venae cava, in the right atrium and ventricle, and in the pulmonary arterial branches. In 2 of the 9 cases in Group 1, air was also found in the left ventricle and coronary arteries. In the surviving cases in all groups the findings were determined by the time of the necropsy following the air embolism. When this was carried out within 15 to 20 minutes, small amounts of air were usually found in the great veins, right heart, pulmonary conus and pulmonary artery. The body of the right ventricle always contained the least amount of air. When the time interval was longer air was not demonstrable.

G. BIPLANE FLUOROANGIOCARDIOGRAPHIC STUDIES demonstrated that air was trapped in the right ventricular outflow tract and pulmonary artery as previously postulated by us[8]. In surviv-

ing animals this air was present when respiration was resumed following the apnea typical of air embolism. Polypnea persisted for a period of time after the air trap had disappeared. In fatal cases the outflow tract and pulmonary artery remained filled with air. A subsequent publication will deal more fully with these roentgenologic aspects of air embolism.

Discussion. The amount of air necessary to kill dogs when injected intravenously has been estimated by several investigators. Harkins and Harmon stated that the minimum lethal dose in one anesthetized dog was 8 cc./kg. when the total amount of air was injected within 20 to 30 seconds. Richardson *et al.*[28] found that the *rate of injection* was of great importance and that very large doses could be tolerated when injected slowly. They also found that anesthesia increases the dog's tolerance to intravenous air. Wolffe and Robertson[32] reported one dog out of an unspecified number of experiments that tolerated 15 cc./kg. after a long series of daily injections in which the dose was gradually increased. No statement is made concerning the position of the animal in any of these reports.

In our experiments the average lethal dose for dogs in the supine position was found to be between 5.0 and 7.5 cc./kg., since the majority of the animals receiving the latter dose died, whereas almost all of those receiving the former survived. The rate of injection was very rapid (1 to 5 seconds). The advantage of the left lateral position, either when the air is injected, or of being turned into that position within 30 to 60 seconds after the injection, is well demonstrated by these experiments. At a dose of 7.5 cc./kg. the chances of recovery are approximately doubled since the survival rate is only 30% in the supine position, while it rises to approximately 60% when the left lateral position is used before or soon after the injection. These results are statistically significant.

The pathophysiology of the dramatic respiratory and circulatory effects associated with venous air embolism has been the subject of many previous investigations. In our own earlier study[8], we pointed out that an air trap develops in the outflow tract of the right ventricle which acts as an effective circulatory block, and that this air trap is especially important when the animal is on his back or on the right side, since, in these positions, the conus region is superiorly located with respect to the remainder of the lesser circulation. In the left lateral position the right ventricular outflow tract is inferior to the body of the right ventricle, and we postulated that the displacement of the air trap by the principle of air bouyancy accounted for the improvement which often occurred when animals were turned into this position after air embolism. The roentgenographic and postmortem studies in the present investigation have confirmed the existence of this air trap. That the presence of a trap in this location does not imply a fall in pulmonary arterial pressure is indicated by the fact that, on the contrary, it invariably rises, as has been indicated previously by Wiggers[31], and as our experiments also demonstrate. Evidently there occur obstructive phenomena both in the peripheral pulmonary circulation and in the right ventricular outflow tract, and the fact that the latter plays an important role is indicated by the significant reduction in mortality associated with displacement of this portion of the obstruction by left lateral positioning.

The late secondary rise in pulmonary arterial pressure occurring after the decline from the initial rise has several possible explanations. The first of these involves a neurogenic mechanism. It is known that active vasoconstriction

of small pulmonary vessels can take place[30], and there is evidence that stimulation of neuroreceptors in the walls of the pulmonary vascular system may elicit a massive reflex vasospasm[16,29]. It is possible, then, that the air in the pulmonary vessels may act in such manner as to initiate these reflexes. The bigeminal rhythm which coincides with the secondary pressure rise might well be considered as lending some support to the presence of an increased sympathetic discharge at this time. On the other hand, there have been some investigators who, working with starch suspension embolization[11], have been unable to note any influence of neurogenic factors in this type of embolism since bilateral cervical vagotomy and bilateral stellate to fifth cervical ganglionectomy has had little effect on mortality when usually fatal doses of starch are used.

Another possible explanation for the secondary pressure rise is one which may not involve a neurogenic mechanism at all, or which may act in conjunction with the aforementioned neurogenic factors. This concerns the mechanical effect of additional doses of air pumped from the right ventricle into the pulmonary circulation. Such additional air may be derived from the aspiration of reservoirs in the cavae when there is a resurgence of respiratory activity, or, in the animals turned onto the left side, it may be that air which has returned, with positioning, from the outflow tract to the body of the right ventricle, and which has then been pumped gradually into the pulmonary artery as froth with the blood.

Finally, it is possible that the secondary rise in pressure (as well as the initial rise) may be due to local anoxia distal to the air bubbles in the pulmonary vessels acting upon them in such a manner as to increase their tone. The possibility that such a mechanism exists is not invalidated by the fact that our studies show no evidence of general anoxemia.

Heparinization in these experiments rules out the remote possibility that clot formation has resulted in the elaboration of a vasconstricting chemical such as serotonin, which Comroe[6] has indicated may act as an important factor in thromboembolism.

The secondary rise in pulmonary arterial pressure, coincident with polypnea and bigeminus, was seen in almost all of the animals which survived, regardless of their anatomical position, but it was seen most often in the group in the left lateral position, since it was in this position that survival rates were greatest. It occurred equally in those which were in the left lateral position throughout the experiment and in those which were turned into this position after receiving the air. The secondary rise, therefore, does not depend on change of anatomic position, but rather on sufficient length of survival for the factors mentioned above to come into play.

The extrasystoles which occurred early in association with the primary rise in pulmonary arterial pressure, and which recurred in bigeminal arrangement during the secondary rise, could not be attributed to the existence of foci of myocardial irritability due to general anoxia, since no such anoxia could be demonstrated at these times and there was no sudden change in carbon dioxide concentration[9]. It is very possible, however, that they were related to localized right ventricular ischemia, as described in a previous publication[8], an ischemia which is the result of a marked drop in coronary flow gradient and a greatly increased right ventricular work load. The type of extrasystolic complex found in our tracings confirms our previous report[26] that these are of right ventricular origin. The S-T segment changes were likewise the same as previously de-

scribed[8] and are related to current of injury flowing in the area of right ventricular ischemia.

The systemic hypotension, bradycardia and biphasic respiratory responses seen in our animals simulate the veratridine reflexes[1,2,18] and the pressoreceptor reflexes recently studied by Aviado *et al*[1]. Veratridine introduced directly into the pulmonary circulation produces, first, a period of apnea, followed thereafter by rapid, shallow breathing. With venous air embolism the results are the same except for the usual occurrence of a very brief polypnea or hyperpnea prior to the apneic period. The polypnea or hyperpnea may be dependent on a carotid sinus mechanism related to the abrupt fall in systemic arterial pressure which occurs coincidentally.

The possible relationship to pressoreceptor reflexes is indicated by the fact that systemic hypotension, bradycardia and accelerated breathing have been produced experimentally[1] by elevations of pressure confined to the right atrium and pulmonary conus, areas wherein pressure elevations characteristically occur in venous air embolism, as has been already indicated. When pulmonary pressure is raised by means of perfusion restricted to the pulmonary artery and vein, polypnea and hypotension occur, but without bradycardia[1], and these effects are eliminated by bilateral vagotomy. In our experiments, when air was injected by means of a catheter directly into the pulmonary artery, an identical hypotension and persistent polypnea, without bradycardia, were obtained, and these effects were likewise eliminated by bilateral vagus section. It is not necessary, then, for air emboli to come into contact with the heart chambers to produce hypotension and polypnea. Conversely, the fact that air which does enter these chambers is associated with such effects does not necessarily indicate that reflexes from the heart chambers are instrumental, since such air rapidly enters the pulmonary vessels where receptors might be stimulated.

Both veratridine and pressoreceptor reflexes are more potent when the stimulus is from the pulmonary veins[1]. In some of our animals there was a definite rise in pulmonary venous pressure during air embolism, but this did not occur in all instances in which this measurement was made. In those in which it did rise, the venous receptor stimulus may have been responsible, in part at least, for the reflex circulatory and respiratory effects.

The mechanism responsible for the rise in pulmonary venous pressure in some of our experiments is unknown. It is possible that it was the result of left ventricular failure due to the diminished coronary flow gradient with consequent left ventricular ischemia. On the other hand, it may have been that, despite the blockade of many pulmonary vascular channels by air, there was an opening of many new channels or arterio-venous anastomoses through which the elevated pulmonary arterial pressure could be transmitted to the veins. The easy distensibility of pulmonary vessels is a well established fact. It is of interest that when starch emboli are injected into animals in amounts insufficient to be responsible for death, the systemic arterial pressure remains at or above normal for an hour, and during this time there is no great permanent diminution in the amount of blood passing through the lungs[7]. With larger doses of starch granules this does not occur, presumably because the obstruction is so complete that no by-pass channels are available. In those of our air embolism experiments in which the pulmonary venous pressure was unchanged or lowered, it is possible that such complete obstruction did occur, but this did not preclude recovery by any means.

It should be emphasized that the duration of the characteristic preliminary polypnea and following apnea were short. The usual duration of these two phases was less than one minute, and always it was less than 2 minutes. Since apnea was present in almost all of the experiments, the results in this one respect are more like those due to veratridine than those due to pressoreceptor stimulation. The polypnea which followed the apnea was of long duration. It lasted up to at least 15 minutes in the surviving cases. This was much longer than the duration of the secondary rise in pulmonary arterial pressure with which the onset of the polypnea was associated. This rise might be considered to have been responsible for the polypnea in the beginning. In pea seed and starch granule embolism it is known that the onset of tachypnea and dyspnea also coincide with the rise in pulmonary arterial pressure[21,22]. The short secondary rise in pressure in air embolism, however, could not account for the continuing polypnea of much longer duration. It is possible that the pulmonary receptors may be stimulated by the mere presence of air emboli even after the pressure has returned to control values.

Preliminary vagotomy in our experiments entirely eliminated the respiratory and circulatory effects from the introduction of small doses of air (up to 1 cc./kg.) into the pulmonary vessels. It did not, however, prevent the abrupt fall in blood pressure or the brief hyperpnea and ensuing apnea which were seen when 7.5 cc./kg. of air were introduced into a peripheral vein. In the latter group, however, when, and if, the animal commenced to breathe again following the apneic period, the vagotomy did seem to be responsible for hyperpneic, rather than polypneic respiration. This effect of vagotomy is true in most forms of tachypnea, either peripheral or central[21,22,30]. We must conclude, then, that while the respiratory and circulatory effect of small doses of air can be eliminated entirely by circumventing vagally-transmitted reflex phenomena, this does not hold true with larger doses. In the latter we must conclude that, neglecting a possible reflex by way of sympathetic chains, the major factor in the respiratory and circulatory difficulties is a mechanical blockade in the pulmonary circulation. This produces an acute depression of cardiac output into the systemic circulation and accounts for the sudden fall in systemic pressure. Since the carotid sinus nerves are intact, a fall of pressure within the sinus could account for the initial hyperpnea. Observations on experimental embolism with Penrose tubing, pea seeds and starch support the concept that reduced output is of great importance and emphasize decreased coronary flow as a contributing factor[22]. The resemblance of pulmonary embolism to myocardial infarction has been stressed by Horn *et al.*[17], and by others. Insofar as venous air embolism has a bearing on the general subject of pulmonary embolism, our experiments would tend to indicate that either reflex or mechanical factors, or both, may be important when the pulmonary circulation is acutely obstructed, and that the two schools of thought[11], reflex and mechanical which have debated this subject, may be reconciled on this basis.

Necropsy examinations following our experiments showed that 7.5 cc./kg. of air by femoral vein is largely eliminated from the heart in 15 minutes and completely so within 30 minutes in surviving animals. There was no evidence that oxygen lack or changes in carbon dioxide concentration played a role in the circulatory or respiratory effects. This is in accord with the experience of others in experiments dealing with

embolism of other types[21,23,30]. Anesthesia as used in this study has been shown to have little effect on dynamics following embolism[22].

We were able to confirm the conclusion of Richardson *et al.*[28] that death in venous air embolism is characterized by primary respiratory failure. The heart continues to beat long after respiration has ceased. The practical implication of this for human air embolism accidents is obvious.

In closing it should be pointed out that our air injections were quite large and were given rapidly. The conditions of the experiment were not dissimilar, however, from the circumstances under which accidental air embolism has occurred in association with various therapeutic and diagnostic procedures in medical practice. They are entirely different, on the other hand, from the therapeutic use of oxygen by very slow intravenous injection which has been advocated by some investigators for the treatment of pulmonary insufficiency[19,33]. The rate of injection of gases into the venous system is very important[19,28,33].

Summary. In a series of venous air embolism animal experiments, it was demonstrated that there is a significant difference in survival rates between the left side down position and the supine or right side down positions. In the former position, at doses of 7.5 cc./kg., the chances of survival were doubled. This was true whether the animal was in this position at the time of embolism or was turned into it within one minute after injection.

Studies relative to the pathophysiology of venous air embolism showed that there occurs immediately following the air injection an abrupt rise in pulmonary arterial pressure and an equally abrupt fall in systemic arterial pressure, associated with an apparent bradycardia due largely to abortive beats which failed to open the aortic valve. In addition to the rise in pulmonary arterial pressure due to peripheral obstruction of this portion of the circulation, there was evidence of an air trap in the right ventricular outflow tract which constituted a further obstructive mechanism, displacable by appropriate positioning. In surviving animals there occurred a secondary rise in pulmonary arterial pressure, accompanied by polypnea, bigeminal rhythm and apparent bradycardia. The pulmonary venous pressure was found to be elevated in many, but not all, instances. The characteristic respiratory pattern was found to be an initial short period of polypnea or hyperpnea, followed by brief apnea and then a long period of polypnea. The possible mechanisms involved in these circulatory and respiratory disturbances are discussed, and reasons are presented for believing that they depend both on reflex (veratridine-like and pressoreceptor reflexes from the heart and pulmonary vessels) and on mechanical factors.

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JET INJECTION OF RADIOISOTOPES

A clinical study comparing needle and jet injection of I_{131}, K_{42} and Na_{24}

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SEVERAL studies of the rate of disappearance from the site of injection of small quantities of gamma-emitting radioisotopes, such as radioiodine and radiosodium, have been made in animals and humans[2,4,5,6,7,8,9,10,11,12,13]. When a hypodermic needle is used for the injection, it is generally assumed that much of the injected fluid forms a local pool. Thus, the surface area and the geometrical configuration of this pool will probably influence the rate of absorption of the tracer isotope. Recently a jet injector*** was made available to us, on an experimental basis, with injectors and loading facilities for the ampules ("metapules") used in the injector. This device can introduce about 1 cc. of solution interstitially in the form of a fine, high speed jet of liquid that penetrates the skin through a very small hole. Preliminary tests in animals have indicated that most of the fluid diffuses into the tissues at a depth of an inch or so below the surface and does not form an appreciable pool[2]. If this is so, the rate of disappearance from the site of injection should be more uniform and meaningful with the jet injector than with the needle. The initial phase of this investigation was directed toward making a direct comparison of rate of disappearance between these two modes of injection, using 1 cc. of solution in each case. The preliminary experiments showed that the disappearance rates, using the jet injector, were much more uniform than similar injections given by needle. Therefore, the investigation was expanded to correlate variation in disappearance rate with various clinical conditions, using the jet injector. Some preliminary results with jet injection of I_{131}, K_{42} and Na_{24} in amounts of about ½ microcurie were obtained. These dosages gave counting rates readily measurable with accuracy, using a wide angle calcium tungstate scintillation counter[1].

Procedure. About ½ microcurie of carrier-free I_{131} in physiological saline was administered to a group of healthy controls by means of the jet injector at a point on the thigh about 5 inches above the knee. The subject was seated so that the surface of the thigh was horizontal. The wide angle scintillation counter was lowered so that its window was within a few millimeters of the skin.

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*** "Hypospray": R. P. Scherer Corporation, Detroit, Mich.

Initial counts of 75 to 100 per second were readily obtainable. The net count was recorded and plotted on semilogarithmic paper against time in minutes. The disappearance rate of the isotope was measured as a "half-time," that is, the number of minutes required for the initial count to decrease to one-half[9].

Material. Ten male and 17 female healthy volunteer control subjects were administered about ½ microcurie I_{131} in 1 cc. of normal saline by jet injector into the left thigh. Some of these subjects also received an intramuscular needle injection of a similar amount of I_{131}, in the identical quantity of normal saline, into the other thigh. A thyroid function test, using I_{131}, was normal in all of the healthy volunteers.

The patient material consisted of 11 male and 3 female patients with hyperthyroidism, 6 male patients with myxedema, 9 male patients with congestive heart failure from various types of heart disease and 10 male patients with previous congestive failure who at present are fully compensated.

In addition to I_{131}, K_{42} and Na_{24} were administered in the same manner to some of the control subjects and patients in quantities of approximately ½ microcurie in 1 cc. normal saline.

Results. I_{131}. In all the jet injection tests the semilogarithmic plot could be approximated closely by a straight line. This means that the jet-injected isotope disappears exponentially from the site of injection until the counting rate is not readily distinguishable from the background. The results obtained with needle injection were variable. Sometimes they did not show an exponential disappearance and very frequently the "half-time" of disappearance was considerably longer than that of the corresponding jet injection test.

Table 1 shows the "half-times" measuring the time elapsed from the number of counts in the thigh immediately after injection to half the number of counts remaining. The range is 7 to 17 minutes in our male controls and 7 to 22 minutes in our female controls. There is more spread in the female series. In the patients with hyperthyroidism, uncomplicated by congestive heart failure, the "half-times" are in the same range as the normal controls.

TABLE 1.—"HALF-TIMES" OF ABSORPTION OF I_{131} INJECTED BY "HYPOSPRAY"

	Number		*Range (minutes)*	
	Males	*Females*	*Males*	*Females*
Healthy controls	10	17	7–17	7–22
Hyperthyroidism	11	3	8–18	9–12
Hypothyroidism	6	—	18–60+	—
Cardiacs, compensated	10	—	10–32	—
Cardiacs, decompensated	9	—	17–38+	—

Nine patients with clinically demonstrable edema, who were in congestive heart failure, had markedly prolonged "half-times" (17 to 38 minutes). The 10 patients with previous congestive failure, but who now were fully compensated clinically, also had prolonged "half-times." The patients with myxedema had markedly prolonged "half-times," from 25 to 60 minutes, plus. (The experiment was terminated after 60 minutes.) Three of these patients were studied repeatedly. As the myxedema was reversed by adequate thyroid medication, their "half-times" returned to within the normal range (Table 2). Fig. 1 demonstrates these relationships.

TABLE 2.—MYXEDEMA. "HALF-TIMES" OF ABSORPTION OF I_{131} USING "HYPOSPRAY"

	(Minutes)	
Patient	*Before* R	*After* R
G. P.	60+	14
R. B.	33	12
J. B.	24	17

Na_{24} and K_{42}. The control subjects and patients who received I_{131}, K_{42} and Na_{24} by jet injection demonstrated very good correlation in their "half-times" (Table 3). The disappearance was exponential with all isotopes used.

Discussion. These preliminary data indicate that the disappearance rate, measured as the "half-time," is much more uniform following administration of isotopes by jet injection than it is following administration by hypodermic needle. The complexity of the problem can be appreciated when it is considered that McGirr[9], using Na_{24}, found differences in "half-time" up to 9 minutes between the left and the right limbs of the same individual at the same session. Hyman and his group[7], in a study involving radioactive sodium, stated that "there is considerable variation between individual subjects with regard to the removal rate."

Another major problem in the technical aspects of tissue clearance is the question of subcutaneous and intramuscular injection. Kety[8] found that the Na_{24} tissue clearance from tissue in man is proportional to the amount of Na_{24} at the site of injection and, therefore, a straight line when plotted on semilogarithmic paper. Wisham and Yalow[13] confirmed these observations but stated further that only after subcutaneous injection could they obtain a straight line and that after intramuscular injection that was not the case. Franke and his group[6], in experiments on dogs, advised the subcutaneous route because of the same considerations, namely the exponential disappearance of Na_{24} which they failed to demonstrate after intramuscular injection.

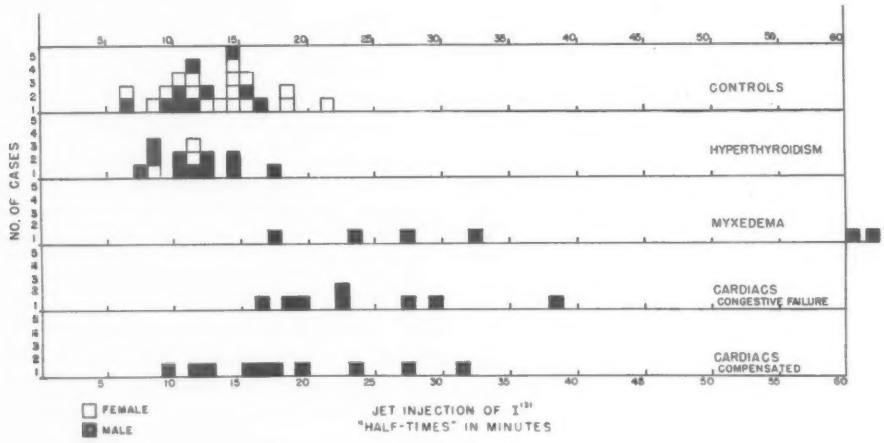

Fig. 1

There is diffusion of the isotope into the tissues. This has been demonstrated in experimental studies in animals[2]. Measurements of the disappearance rate are therefore more valid than those obtained following subcutaneous and intramuscular injection by hypodermic needle.

The "half-times" of all our control subjects, using I_{131}, correspond to those obtained by McGirr with Na_{24} (6 to 25 minutes for gastrocnemius muscle, 10 to 44 minutes from skin) although there is less spread in our series.

The "half-times" in the female controls are somewhat longer and more

spread out than in the males. The reason for this is not clear. The menstrual histories are being investigated to determine whether any correlation exists.

Patients with cardiac failure and edema had prolonged "half times" with I_{131}. Of great interest is the observation that 10 patients with fully compensated heart disease, but with previous congestive failure, also showed long "half times." Discussion of these findings is beyond the scope of this preliminary communication and will be offered in a subsequent publication with additional studies.

In a few preliminary experiments, I_{131}, K_{42} and Na_{24} were administered by jet injection to the same individuals and a striking correlation of the "half-times" was observed. This suggests that isotopes of low atomic weight in the ionic form may be used interchangeably for tissue clearance determinations. Boatman *et al.*[3] suggested this in their work on cerebral and muscle clearance, using I_{131}, Na_{24} and P_{32}.

Summary. 1. I_{131} in amounts of ½ microcurie was injected by hypodermic needle and by jet injection ("Hypospray") into the thighs of healthy control subjects and patients with a variety of clinical conditions.

2. The disappearance rate of the injected isotope as measured with the wide angle scintillation counter was

TABLE 3.—COMPARISON OF "HALF-TIMES" OF ABSORPTION OF I_{131}, K_{42} AND Na_{24}, INJECTED BY NEEDLE AND HYPOSPRAY

		"Half-time" in Minutes			
		Needle	*Hypospray*		
Name	*Diagnosis*	I_{131}	I_{131}	K_{42}	Na_{24}
F. B.	Control	22	12	14	15
B. C.	Control	39	11	14	13
B. S.	Control	14	12	12	11
J. E.	Control	35	7	14	18
E. Y.	Control	17	15	16	—
A. S.	Hyperthyroidism	—	9	—	9
C. D.	Hyperthyroidism	23	11	—	—
N. M.	Hyperthyroidism	9	11	—	—
S. H.	Hyperthyroidism	9	8	—	—
S. N.	Hyperthyroidism, treated, euthyroid	32	17	—	—
L. N.	Hyperthyroidism, thyrocardiac, treated, euthyroid, compensated	16	10	—	—
W. K.	Hyperthyroidism, treated, clinically slightly hypothyroid	23	15	—	—
J. K.	Hyperthyroidism, treated, clinically euthyroid	—	12	14	—
N. O.	Pituitary hypothyroidism	—	28	28	—
C. W.	Hypothyroidism	—	31	35	—
J. S.	Coronary artery disease, compensated	—	17	13	—
C. A.	Rheumatic heart disease, compensated	27	13	18	15
M. H.	Cor pulmonale, compensated, previous congestive heart failure	—	24	—	18
J. H.	Arteriosclerotic heart disease, compensated	—	12	14	15
A. D.	Hypertensive cardiovascular disease, compensated	18	17	—	—
N. W.	Hypertensive cardiovascular disease, compensated	—	16	—	19
M. D.	Hypertensive cardiovascular disease, compensated	—	17	—	22
W. D.	Hypertensive cardiovascular disease, decompensated	30	21	—	—
J. M.	Carcinoma of thyroid (euthyroid)	21	10	—	—
J. R.	Carcinoma of thyroid (euthyroid)	—	14	17	—
J. B.	Epilepsy	22	13	—	—

much more uniform after jet injection than after needle injection.

3. K_{42} and Na_{24} in identical amounts were injected by jet into some of the same control subjects and patients, and it was found that the disappearance times were similar to those obtained with I_{131}.

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RESULTS WITH ORAL HEXAMETHONIUM ALONE AND IN COMBINATION WITH 1-HYDRAZINOPHTHALAZINE (APRESOLINE*) IN THE THERAPY OF HYPERTENSION**

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NUMEROUS drugs are available which are capable of reducing blood pressure in patients with hypertension. However, practical therapeutics with many of these compounds is limited because of the development of tolerance, the presence of untoward side effects, or because these agents are destroyed in the gastrointestinal tract and must, therefore, be given parenterally. Preliminary observations[4] indicated that hexamethonium chloride† when administered orally, was an effective agent for reducing the blood pressure in patients with hypertension. It is the purpose of this report to present observations on this compound over an extended period of time and to compare these results with those of other hypotensive agents used in the same clinic. Patients treated with hexamethonium, but in whom adequate regulation of the blood pressure was not obtained were treated with a combination of 1-hydrazinophthalazine* and hexamethonium. These observations are also presented. The studies were conducted on an outclinic basis. Therefore, the problems encountered should closely parallel those which are met in general office practice.

Methods and Materials. A group of 58 unselected ambulatory patients with moderate to severe hypertension were started on oral hexamethonium chloride. This included 40 patients who attended the medical and cardiac clinics and 18 private patients‡. There were 11 additional patients who were lost from the study due to movement from the area or because of unreliability and failure to return to the clinic. All of the patients had blood pressures, as measured in both the supine and upright positions, of 160/100 or greater. There were 28 men and 30 women whose ages ranged from 29 to 71 years. The majority of the patients were

* Supplied by Ciba Pharmaceuticals, Inc. as Apresoline (Ba 5968).

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† Supplied as Methium by Chilcott Laboratories, Inc., Hexamethon by Burroughs Wellcome, Inc., and Esomid by Ciba Pharmaceuticals, Inc.

‡ We extend appreciation to Dr. Charles Armbrust and Dr. Herman Glantzburg for making some of their patients available to us.

followed at weekly intervals for 6 weeks to 3 months before being placed on the drug. During the control period, and every one to 2 months thereafter, they were subjected to the following laboratory tests for evaluating patients with hypertension: electrocardiogram, chest roentgenogram, eye ground examination, routine urinalysis, urine concentration, phenolsulfonphthalein excretion, urea clearance, and blood urea nitrogen determination. Following the control periods, during which time the patients received only supportive therapy and placebo medication, they were placed on oral hexamethonium chloride and were followed at weekly or semi-weekly intervals still as outpatients. A small number of the more ill patients were hospitalized during the control period as well as during the induction of drug therapy. The length of the control period in these patients varied with the urgency for beginning hypotensive therapy. The control as well as the follow-up blood pressure determinations were taken both in the supine and upright positions at the time of the weekly visits of the patients to the clinic. This is necessary because of the orthostatic hypotensive response to most of the ganglionic and adrenergic blocking drugs. The blood pressure was determined by the physician (investigator) on each clinic visit, as well as by the nurse at the time the patient registered in the clinic and several hours later just prior to the patient's return home. These additional observations offered some opportunity for evaluating variations in blood pressure between doses of the drug. The control supine and upright blood pressure for each patient as recorded in Table 2 was determined by taking the average of all blood pressure determinations during the control period in each position. The post-drug blood pressure is the average of the values obtained in both the supine and upright position after the therapeutic dose for each patient was established; that is, after the titration period (during which time the blood pressure and drug dosage were being stabilized). The number of post-drug observations of necessity depends on the length of the follow-up period. The initial dose of hexamethonium was 250 mg. given orally 4 times per day, before each meal and at bedtime. This was gradually increased in a stepwise fashion until an adequate response was obtained or until side reactions forced discontinuance of the drug. The morning and evening doses of the drug were increased first. The midday and night doses were next increased. It was felt that this routine maintained as constant a blood concentration of hexamethonium as possible if the dosage schedule was to remain practical for long term therapeutic purposes. Mealtime was a good reminder to the patients to take their medicine. In addition, the taking of the medication along with food was found to decrease the rapidity of absorption and thus maintained a more constant hypotensive response. Whether or not the drug was taken along with food, it was found highly essential that the drug be taken with the same relationship to meals from day to day if the blood pressure was to be well regulated. For example, syncope due to excessive hypotension was frequently observed if the drug was taken on an empty stomach after the patient had previously been taking it along with his meals. During the titration period, one week was usually allowed before changes in the dosage schedule were made, unless the patient was in the hospital. In addition to the observations on blood pressure, clinical manifestations of excessive hypotension such as dizziness on standing and weakness were taken into consideration when regulating the dosage schedule. There is no doubt that a more constant blood level of such drugs as hexamethonium can be maintained if they are administered every 3 to 4 hours around the clock as advocated by Schroeder[12]. However, most of our patients objected to this routine and could not be fully depended upon to take their medication on a 4-hour schedule, particularly at night. Because of the psychogenic aspects of hypertension, and because too much of the patient's attention has already been focused on his or her disease, such considerations become of utmost importance. We feel that if the therapeutic program is too cumbersome, it defeats its own purpose. However, several of the more seriously ill hypertensive patients who displayed excessive variation in blood pressure between doses of hexamethonium were given the drug in smaller amounts more frequently. The period of follow-up on the patients herewith presented varied between 4 and 16 months.

Patients in whom adequate blood pressure regulation was not possible with hexamethonium alone were placed on combined hexamethonium and Apresoline (1-hydrazinophthalazine) therapy. The hexamethonium was progressively increased until side

reactions were manifested. If adequate control of the blood pressure was not obtained, the dose was reduced slightly and Apresoline was started. This drug was titrated in a similar fashion to hexamethonium. The original dose was 25 mg. 4 times a day. The dose was increased in 25 mg. increments at weekly or semi-weekly intervals.

Results. For purposes of analysis, the 58 patients on whom adequate follow-up could be maintained have been divided into 3 groups according to the diastolic blood pressure. Group 1 consists of 16 patients with the most severe hypertension in whom the average diastolic pressure during the control period was more than 140 mm. Hg. Group 2 consists of 27 patients in whom the control diastolic pressure was more than 120 but less than 140 mm. Hg, and Group 3 includes 15 patients with the least severe hypertension in whom the diastolic blood pressure was more than 100 but less than 120 mm. Hg. The severity of the hypertension and the great number of complications in these patients can easily be deduced from the observations summarized in Table 1. About one-fourth of the patients had severe renal damage, and another one-fourth had minimal to moderate impairment of renal function prior to therapy as indicated in the renal function studies employed. All of the patients with severe renal damage fell into Groups 1 and 2, evidence of the severity of the disease in these 2 groups of patients. The blood urea nitrogen was moderately elevated (above 30 mg. per 100 cc.) in 3 patients in Group 1 and in 3 patients in Group 2. Numerous red blood cells were found in the urine of 8 patients. These observations did not necessarily indicate that renal disease preceded the hypertension. More likely the reverse was true in most instances since patients with frank evidence of acute or chronic nephritis were not included in the study. Five of the patients in Group 1 and 6 in Group 2 were classified as malignant hypertension.

About one-fourth of the patients had evidence of congestive heart failure (Table 3). This had already been treated prior to receiving hexamethonium in most instances. In a few of the patients with less severe failure, cardiac therapy was not inaugurated in order to evaluate the effect of blood pressure reduction alone on the clinical course of heart failure. Fourteen patients complained of precordial pain prior to therapy. This was typically anginal in type in 7 patients. Three patients had previously had myocardial infarctions. The electrocardiogram during the control period was interpreted as being abnormal in 46 patients included in the present study. In 22 there was only evidence of left ventricular hypertrophy, whereas in the remaining 24, there was evidence of frank myocardial damage. Cerebrovascular disease was present in 10 patients as evidenced by previous cerebral arterial occlusions or hemorrhages or by the presence of encephalopathic manifestations.

The blood pressure responses of the 3 groups of patients are presented in Table 2 (A-C). The period of follow-up after receiving hexamethonium varies from 4 to 16 months. The observations on blood pressure presented in Table 2 (A-C) are the average values for each patient before and after hexamethonium. A reduction in mean blood pressure* of 20 mm. Hg or more was considered to be a significant response to the drug. The mean values but not the individual observations for the unresponsive group of patients are also presented. There were about twice as many patients in Group 2 (diastolic 140 mm. Hg) as there were in either pressure more than 120 but less than

* Diastolic blood pressure plus one-third the pulse pressure.

TABLE 1.—SUMMARY OF CLINICAL STATUS OF THE HYPERTENSIVE PATIENTS TREATED AND AN ANALYSIS OF SOME OF THE COMPLICATIONS OF THEIR DISEASE PRIOR TO RECEIVING HEXAMETHONIUM ORALLY

		Vital Data					*Electrocardiogram*			*Pretreatment Complications*							
		Race		*Sex*										*Renal Damage*			
	No. Pts.	*W*	*C*	*M*	*F*	*Age*	*Norm.*	*Left Vent. Strain*	*Myocardial Damage*	*None*	*CVD‡*	*Heart Failure*	*Precordial Pain*	*0*	*++*	*+++*
Group 1*																
Responsive	13	3	10	9	4	47	1	4	8	4	2	3	3	6	3	4
Unresponsive	3	2	1	1	2	64	1	—	2	—	1	1	1	—	2	1
Group 2**																
Responsive	22	12	10	12	10	50	2	12	8	10	3	7	4	12	4	6
Unresponsive	5	1	4	1	4	51	1	2	2	1	2	2	2	1	2	2
Group 3***																
Responsive	12	6	6	3	9	52	3	4	5	4	1	2	3	10	2	—
Unresponsive	3	2	1	2	1	56	1	—	2	—	1	1	1	3	—	—
Total	58	26	32	28	30		9	22	21	19	10	16	14	32	13	13

* Patients with diastolic blood pressure more than 140 mm. Hg.
** Patients with diastolic blood pressure more than 120 but less than 140 mm. Hg.
*** Patients with diastolic blood pressure more than 100 but less than 120 mm. Hg.
‡ CVD—Cerebrovascular disease.

Groups 1 or 3. The amount of drug required to reduce the blood pressure was apparently not dependent on the degree of blood pressure elevation since the average daily dose was just as large for the patients in Group 3 as for those in Group 1. However, patients with the clinical syndrome of malignant hypertension were more difficult to regulate, particularly if the hypertension was associated with heart failure. This may be due to altered and erratic gastrointestinal absorption of the drug in patients with heart failure. Patients who were considered unresponsive to the drug usually received as large as or larger daily amounts than the responsive patients. There was no evidence to indicate that increasing amounts of hexamethonium (development of drug tolerance) were required to maintain a hypotensive response after the initial induction period since the patients who were treated for 9 months to a year or more did not require more drug than they did during the first 3 months. There were exceptions, in that some of the patients required more drug per day than they did initially, but just as many required less. One of the most annoying problems encountered was variability in the hypotensive response from time to time, although the dose was not altered (Fig. 1). This variation was decreased by taking the medication along with meals in order to obtain a slower and more constant rate of absorption. It was also noted that during periods of increased activity or hot weather the drug requirement decreased, probably a result of decreased excretion (Fig. 1).

Reduction in blood pressure was greater in the upright position than in the supine. Percentagewise, there was an equivalent decrease in both the systolic and in the diastolic pressures. Tachycardia usually did not accompany the reduction in blood pressure, probably because the drug blocks off the sympathetic innervation to the heart. Of a total of 58 patients, 47 (81%) (Tables 1 and 6) initially showed a significant reduction (decrease in mean blood pressure of 20 mm. Hg or more) in blood pressure in the upright position, without prohibitive side reactions. The blood pressure was reduced to normotensive limits (less than 150/100) in 27 (47%) of the patients (Table 6). The 11 unresponsive patients (19%) presented side reactions that were considered by the therapist to be serious enough to warrant altering the therapy, before adequate reduction in blood pressure was attained. These unresponsive patients were started on the combined Apresoline (l-hydrazinophthalazine) and hexamethonium regimen. Patients with renal disease appeared to respond equally as well as those without evidence of renal disease. Percentagewise, as many patients with diastolic blood pressures above 140 responded as those with diastolic pressures between 100 and 120 mm. Hg, but a reduction in pressure to normotensive ranges was obtained in a higher percentage of patients in the latter group. Patients with highly malignant hypertension showed more variability from week to week than those with less severe disease and consequently were more difficult to regulate. The complication of heart failure in patients with malignant hypertension further increased the difficulty of regulating the blood pressure.

After prolonged periods of observation, analysis of the results show that 4 patients (Nos. 17, 22, 44, and 52) who obtained a reduction in blood pressure initially have discontinued therapy on their own accord after periods of 4 to 11 months, despite the fact that the blood pressure (upright) was maintained within normotensive ranges as long as the patients continued to

TABLE 2A.—BLOOD PRESSURE RESPONSE AND CLINICAL FOLLOW-UP TO TREATMENT WITH HEXAMETHONIUM CHLORIDE (ORAL)

Group 1. Patients with control diastolic pressure above 140 mm. Hg.

Patient Number	Upright B.P. C S	Upright B.P. C D	Upright B.P. D_1 S	Upright B.P. D_1 D	Upright B.P. % of Control S	Upright B.P. % of Control D	Supine B.P. C S	Supine B.P. C D	Supine B.P. D_1 S	Supine B.P. D_1 D	Supine B.P. % of Control S	Supine B.P. % of Control D	Dur. Rx	Dose*	Time to** Regulate	Patient's Reaction Good	Patient's Reaction Fair	Patient's Reaction Poor	Present Status Cont. Rx	Present Status Dc. Rx
1	279	148	188	111	67	75	300	152	258	133	86	88	1 yr.	4000	4	X			X	
2†	248	154	219	122	88	79	252	159	241	149	96	94	8 mo.	2000	8			X		X†
3†	250	140	147	116	59	83	250	140	165	118	66	84	9 mo.	1000	4		X			X†
4	238	146	127	95	53	65	240	150	147	105	61	70	1 yr.	3000	12	X			X	
5	230	140	150	90	65	64	230	140	167	102	73	73	15 mo.	2500	4	X			X	
6	230	160	168	127	73	79	230	160	168	117	73	73	8 mo.	3000	2	X			X	
7†	230	140	178	96	77	69	240	140	208	98	87	70	1 yr.	3000	3		X			X†
8	230	164	137	92	60	56	240	160	158	96	66	60	15 mo.	2500	4	X			X	
9	220	158	134	92	61	58	210	158	152	108	72	68	14 mo.	3000	6	X			X	
10	210	150	141	106	67	71	220	160	180	120	82	75	6 mo.	3000	5		X		X	
11	202	148	178	118	88	80	219	150	173	107	79	71	9 mo.	1500	2	X			X	
12	196	150	140	90	72	60	202	148	150	104	74	70	11 mo.	2500	5	X			X	
13	191	146	148	112	78	77	203	176	171	126	84	72	8 mo.	5625	6	X			X	
Mean Responsive (13 pts.)	227	150	158	105	70	70	234	153	180	114	77	74	11 mo.	2817	Total	9	3	1	10	3
Mean Unresponsive (3 pts.)‡	232	157	219	146	95	93	236	156	214	153	91	98	3 mo.	4250	Tota	—	—	3	—	3

C—Control D_1—After receiving hexamethonium but following initial titration period.
S—Systolic D—Diastolic Cont.—Continue Dc.—Discontinue Rx—Treatment

* Milligrams per 24 hours.
** Time expressed in weeks for best blood pressure regulation obtainable for that patient—not necessarily ideal regulation.
‡ One of these patients died with renal failure and uremia.
† 1-Hydrazinophthalazine in addition to hexamethonium (Table 4) was given to this patient in an attempt to better regulate the blood pressure.

TABLE 2B.—BLOOD PRESSURE RESPONSE AND CLINICAL FOLLOW-UP TO TREATMENT WITH HEXAMETHONIUM CHLORIDE (ORAL)

Group 2. Patients with control diastolic pressure above 120 but less than 140 mm. Hg.‡

Patient Number	Upright B.P. C S	Upright B.P. C D	Upright B.P. D_1 S	Upright B.P. D_1 D	Upright B.P. % of Control S	Upright B.P. % of Control D	Supine B.P. C S	Supine B.P. C D	Supine B.P. D_1 S	Supine B.P. D_1 D	Supine B.P. % of Control S	Supine B.P. % of Control D	Dur. R	Dose*	Time to** Regulate (weeks)	Patient's Reaction Good	Patient's Reaction Fair	Patient's Reaction Poor	Present Status Cont. R	Present Status Dc R
17	244	124	140	95	57	77	213	128	171	106	80	83	4 mo.	2500	2			X		X
18	240	130	158	83	66	64	240	130	192	107	80	82	9 mo.	2000	4	X			X	
19	240	136	140	94	58	69	230	140	158	100	69	71	12 mo.	3000	6	X			X	
20	227	138	132	93	58	67	220	150	145	95	66	63	7 mo.	2000	1		X		X	
21	220	120	180	90	82	75	220	120	190	100	86	83	9 mo.	2000	3	X			X	
22	216	129	156	87	72	67	229	125	196	99	86	79	11 mo.	1500	3		X			X
23	215	123	110	62	51	50	233	126	194	104	83	83	4 mo.	3000	3		X		X	
24†	210	128	157	106	75	83	231	127	192	120	83	94	10 mo.	6000	6	X				X†
25†	210	136	169	106	80	78	215	130	182	118	85	91	6 mo.	4000	3		X			X†
26	210	135	190	100	90	74	210	135	170	112	81	83	8 mo.	1500	2	X			X	
27	208	137	124	88	60	64	230	132	142	104	62	79	9 mo.	3000	4		X			X
28	207	136	151	101	73	74	213	135	197	126	92	93	8 mo.	3000	1	X			X	
29†	206	125	158	96	77	77	212	130	164	94	77	72	8 mo.	4000	2	X				X†
30†	203	124	150	106	74	85	183	122	180	114	98	93	8 mo.	4000	4	X				X†
31	200	130	140	98	70	75	200	130	148	96	74	74	8 mo.	4000	3	X			X	
32	200	120	94	70	47	58	210	110	158	88	75	80	5 mo.	2000	3		X		X	
33	194	131	142	100	73	76	200	137	174	120	87	88	10 mo.	2000	2	X			X	
34	193	120	101	78	52	65	205	114	165	99	80	87	5 mo.	500	—		X		X	
35	190	130	140	90	74	69	190	130	165	100	87	77	6 mo.	4000	2	X			X	
36	174	124	112	84	64	68	169	120	146	110	86	92	13 mo.	4000	2	X			X	
37	173	138	110	80	64	58	188	133	152	110	81	83	14 mo.	4000	10	X			X	
38	170	120	127	70	75	58	190	124	150	104	79	84	12 mo.	1000	3	X			X	
Mean Responsive (22 pts.)	207	129	140	90	68	70	211	129	170	106	81	82	8 mo.	2864	Total	14	7	1	15	7
Mean Unresponsive (5 pts.)	216	129	205	129	94	99	219	123	211	123	95	100	3 mo.	3750	Total	—	—	5	—	5

* Milligrams per 24 hours.
** Time for best blood pressure regulation obtainable for the patient—not necessarily ideal regulation.
† Same note as Table 2A.
‡ See Table 2A for key to abbreviations.

TABLE 2C.—BLOOD PRESSURE RESPONSE AND CLINICAL FOLLOW-UP TO TREATMENT WITH HEXAMETHONIUM CHLORIDE (ORAL)

Group 3. Patients with control diastolic pressure above 100 but less than 120 mm. Hg.‡

Patient Number	Upright B.P. C S	Upright B.P. C D	Upright B.P. D_1 S	Upright B.P. D_1 D	Upright B.P. % of Control S	Upright B.P. % of Control D	Supine B.P. C S	Supine B.P. C D	Supine B.P. D_1 S	Supine B.P. D_1 D	Supine B.P. % of Control S	Supine B.P. % of Control D	Dur.	Dose*	Time to** Regulate (weeks)	Patient's Reaction Good	Patient's Reaction Fair	Patient's Reaction Poor	Present Status Cont.	Present Status Dc.
44	235	119	147	86	63	72	261	126	199	96	76	76	8 mo.	4000	3		X			X
45	225	105	148	87	66	83	225	105	188	93	84	89	8 mo.	1250	2	X			X	
46	216	110	161	90	75	82	220	100	197	91	90	91	9 mo.	3000	1	X			X	
47	211	117	141	96	67	82	194	113	148	98	76	87	1 yr.	4000	10	X			X	
48	203	119	170	100	84	84	206	119	178	106	86	89	10 mo.	3750	2	X			X	
49	191	119	140	102	73	86	213	139	170	110	80	79	9 mo.	2700	4	X			X	
50	188	112	138	98	73	88	196	116	158	96	81	83	10 mo.	4000	1	X			X	
51	185	111	130	90	70	81	188	107	188	104	100	97	16 mo.	2700	8	X			X	
52	179	114	124	89	69	78	183	114	145	100	79	88	8 mo.	2500	2	X				X
53	178	116	144	98	81	85	184	120	148	100	80	83	11 mo.	2500	3	X			X	
54	203	114	146	96	72	84	209	118	166	101	79	86	11 mo.	2700	2	X			X	
55	199	110	142	92	71	84	205	114	162	97	79	85	9 mo.	3300	6	X			X	
Mean Responsive (12 pts.)	201	114	144	94	72	82	207	116	171	99	83	86	10 mo.	3033	Total	11	1	—	10	2
Mean Unresponsive (3 pts.)	171	113	151	103	89	91	170	111	162	103	95	93	3 mo.	2500	Total	—	—	3	—	3

* Milligrams per 24 hours.
** Time for best blood pressure regulation obtainable for the patient—not necessarily ideal regulation.
‡ See Table 2A for key to abbreviations.

take the drug. When the drug was abandoned in one of these patients (No. 17), the blood pressure increased rapidly. This was followed by a cerebral hemorrhage and death. Hexamethonium was abandoned in a fifth patient (No. 27) because of a rising blood urea nitrogen.

In addition to the 11 patients unresponsive to hexamethonium alone, Apresoline has been added to the hexamethonium regimen in 7 other patients (Table 2, A-C) because of variability in the blood pressure, because further reduction in pressure was desirable, or because the side effects were such that hexamethonium alone as a permanent type of therapy appeared impractical. These patients had taken the drug for 6 to 12 months, and all of them continued to obtain a reduction in mean blood pressure of 20 mm. Hg or more (Table 1; 2, A-C) which was about equivalent to their original response. In final analysis, a significant blood pressure reduction was obtained initially in 81% of the patients taking hexamethonium orally, but it was a satisfactory method for controlling the blood pressure on a long term basis in only 60% of the patients. At this time, there is no evidence to indicate that the 60% (35 patients) who continue to take hexamethonium will not be able to have their blood pressure regulated with this drug on a permanent basis (Table 6).

The initial side effects associated with hexamethonium therapy were numerous, but in very few instances were they serious enough to cause concern. Simple measures were usually adequate for managing the side reactions. For example, constipation was experienced by most of the patients. Cholinergic drugs were not used for this problem, but cathartics in the form of cascara, mineral oil, bulk laxatives, and milk of magnesia were used freely whenever indicated. Serious side reactions were more likely to occur if the dose of hexamethonium was built up too rapidly. When this was done, the minimum dose was often passed. As a

TABLE 3.—SIDE REACTIONS AND SYMPTOMS RELIEVED BY HEXAMETHONIUM CHLORIDE

	Number Complaining			
	Initial†		*3 Months***	
*Symptoms**	*No.*	*%*	*No.*	*%*
1. Anorexia	25	43	9	19
2. Blurred Vision	34	59	7	15
3. Dry Mouth	26	45	11	23
4. Urinary Retention	3	5	—	—
5. Constipation				
Marked	19	33	6	13
Mild	20	35	18	38
6. Impotence	12	43***	11	39***
7. Nausea	24	41	5	11
8. Vomiting	6	10	2	4
9. Fatigue	27	47	12	26
10. Diarrhea	6	10	5	11
11. Abdominal Cramps	11	19	1	2
12. Dizziness	22	38	14	30
13. Syncope	7	12	3	6
No Symptoms	13	22	19	40

	Symptoms Improved				
		Number Improved			
		Initially		*3 Months*	
Symptom or Sign	*No. with Complaint*	*No.*	*%*	*No.*	*%*
Headache§	22	18	82	16	73
Albuminuria	16	9	56	13	81
Precordial Pain	14	7	50	11	79
Retinopathy‡‡	21‡‡	9‡	43	16‡	76
Hematuria	8	4	50	7	88
Heart Failure	16	8	50	13	81
Nervous Tension	16	11	69	14	88
EKG					
Left Vent. Strain	22	5	23	16	73
Myocardial Damage	24	1	4	5	21

† Incidence in total of 58 patients treated.
* Symptoms Nos. 1–6 probably due to parasympathetic ganglionic blockade; Nos. 7 and 8 to local effect; No. 9 probably due to striated neuromuscular blockade; and Nos. 10–13 due to sympathetic blockade.
** 47 patients.
*** 28 males.
§ Headaches following the onset of hypertension.
‡ Improved to next grade or more according to classification of Keith-Wagener.
‡‡ Includes only those patients with retinopathy of Grade III and IV.

result, excessive reduction in blood pressure was produced and syncope on standing was not infrequent. At the same time, the patients complained bitterly of weakness*, dry mouth, blurred vision and difficulty in defecation*. These all improved as the drug was excreted and the blood pressure rose to normotensive or mild hypertensive levels. Although orthostatic dizziness was experienced at sometime or other by most patients, this cannot be termed a true side reaction, since it merely indicates over zealous reduction in blood pressure. Due to variability in the blood pressure of most patients, an attempt was made to regulate the *upright* blood pressure at 150/100 in order to avoid excessive hypotensive swings and resulting syncopal attacks. Syncope occurred almost invariably if the supine blood pressure was adjusted to strict normotensive levels. Two patients developed temporary intestinal atony and lower abdominal pain that closely resembled large bowel obstruction*. Both patients recovered rapidly upon withdrawal of the drug. Intermittent nausea, occasional vomiting, and diarrhea with abdominal cramps* were seen quite frequently, but usually these were only seen while initiating therapy. Urinary retention* occurred in 3 patients but in each instance the dosage schedule was increased rapidly. Upon discontinuing the drug in 2 patients, this symptom was completely relieved. In the third, the symptom improved after 24 hours, and it was not necessary to alter the therapeutic program. A large percentage of the males experienced some degree of impotence, but no alteration in sexual drive. Attempts to occasionally relieve this symptom by leaving off the night dose proved ineffective unless the blood pressure also escaped from control. Therefore, in most patients with very severe hypertension, it was thought inadvisable to overcome this complaint or to bring the possibility to the patient's attention. Upon discontinuance of hexamethonium, the symptom was always completely relieved. Most of the side reactions to hexamethonium decreased as therapy continued (Table 3). However, even when the patients had been on the drug for long periods of time, if they obtained a marked increase in the hypotensive response to the drug by increased intake, increased absorption or decreased excretion, the previous side reactions frequently returned as the blood pressure dropped. This was particularly true of fatigue, blurred vision and constipation.

The most outstanding symptomatic improvements were the relief of headaches and angina pectoris. This occurred in three-fourths of the patients with these complaints. Relief was just as pronounced after 3 months as it was initially. Eye ground examination in patients with retinal hemorrhages showed definite objective improvement in the majority of patients after 3 months of therapy. This was in the form of reduction of hemorrhages and exudates and frequently improvement in vision. In 21 patients with 3 and 4 plus (Keith-Wagener classification) changes due to hypertensive vascular disease, improvement to the next grade or better was noted in 76%. Papilledema disappeared rapidly in all patients with this complication who obtained a reduction in blood pressure. Hemorrhages also disappeared, but this occurred more slowly, usually over a period of 6 to 12 weeks. Although improvement of phenolsulfonphthalein excretion and urea clearance was observed in only 8 patients, progressive impairment was not observed in any patients as long as the blood pressure could be controlled. The blood urea nitrogen increased in 2 patients and returned to normal ranges in 4 others who showed azotemia during the control studies. One of the patients in

* Hexamethonium was abandoned in 11 patients before a significant reduction in blood pressure was observed due to side reactions consisting of urinary retention in 2 patients, severe constipation in 3 patients, weakness in 1 patient, nausea and vomiting or diarrhea in 4 patients, and excessive variability of blood pressure in 1 patient.

TABLE 4.—RESPONSE OF COMBINED HEXAMETHONIUM AND APRESOLINE THERAPY IN THOSE PATIENTS IN WHOM ADEQUATE BLOOD PRESSURE REGULATION WAS NOT OBTAINED WITH HEXAMETHONIUM ALONE

Patient No.	Diagnosis	Dose C_8*	Dose 5968*	Upright Blood Pressure						Supine Blood Pressure						Comments
				Control		Hex. Cl. Alone		Hex. plus 5968		Control		Hex. Cl. Alone		Hex. plus 5968		
				S	D	S	D	S	D	S	D	S	D	S	D	
2	MHCVD	2000	550	248	154	219	122	196	106	252	159	241	149	220	126	Palpitations, tachycardia. Dc. drug.
3	MHCVD**	1000	600	250	140	147	116	138	98	250	140	165	118	148	106	NTE, better stabilized.
7	HCVD	3000	300	230	140	178	96	138	78	240	140	208	98	170	100	NTE
14	HCVD	3500	600	238	164	210	158	180	108	240	166	234	158	208	120	Severe constipation if dose increased.
16	MHCVD	4000	450	244	148	210	138	172	106	250	144	220	136	196	124	Continued lability of blood pressure.
24	HCVD	6000	400	210	128	157	106	148	88	231	127	192	120	162	110	Headache. Dc. drug.
25	CF, HCVD**	4000	250	210	136	169	106	144	96	215	130	182	118	158	100	Slight diarrhea.
29	MHCVD	3000	200	206	125	158	96	140	82	212	130	164	94	160	90	Better stabilized.
30	CF, HCVD**	4000	200	203	124	150	106	143	96	183	122	180	114	176	110	NTE, better stabilized.
40	CF, HCVD	2000	200	200	138	179	127	156	107	187	132	167	130	154	110	Headache.
41	HCVD	2500	750	261	138	232	136	143	93	281	148	226	147	153	99	Weakness.
Mean		3182	409	227	140	183	119	154	96	231	140	198	126	173	109	
Mean of unresponsive to both C_8 and Apresoline (7 pts.)		3168	842	228	142	212	137	215	136	245	143	231	138	214	134	

MHCVD—Malignant hypertensive cardiovascular disease.
CF—Cardiac failure.
HCVD—Hypertensive (essential) vascular disease.
NTE—No toxic effects.
S—Systolic
D—Diastolic

* Dose in milligrams per 24 hours.
** Excessive lability of blood pressure with hexamethonium alone—lability greatly reduced when Apresoline was added.

whom the blood urea nitrogen increased was a patient with malignant hypertension in Group 1 who obtained a reduction in blood pressure initially, but later broke out of control. Apresoline was added to his therapy also, to no avail, and he died with progressive renal failure. The other patient showing a rising blood urea nitrogen during the study was in Group 2. Because of the increasing azotemia, hypotensive therapy had to be abandoned. Albumin and red cells in the urine which were observed during the control studies in some of the more severe hypertensive patients were relieved in 81 and 88% of cases respectively. This was particularly true in the case of intermittent hematuria which accompanied exacerbations in the hypertension. After 3 months of hypotensive therapy, the symptoms and signs of heart failure improved as the blood pressure was reduced in about 81% of the 16 patients with this complication. Improvement occurred in those patients receiving digitalis or diuretics as well as in those patients not receiving collateral therapy for heart failure. This was accompanied by decreased heart size on roentgenograms in many instances. The blood pressure in patients with simultaneous cardiac failure and marked renal disease was particularly difficult to regulate, however. In general, the electrocardiograms which showed a left ventricular strain pattern improved (73%). If myocardial damage was marked, very little improvement of the electrocardiographic pattern was observed. During the course of this study, 2 patients who responded to treatment for a short time, broke out of control, rapidly progressed downhill and died. One of them died because of a cerebral hemorrhage (No. 39) and the second (No. 15) because of progressive renal disease. Both of them had malignant hypertension with advanced renal disease and heart failure. Combined hexamethonium and Apresoline was no more effective in regulating the blood pressure in either one of these patients than was hexamethonium alone. The third death that was observed in the present study was due to a cerebral hemorrhage which followed a sudden rise in blood pressure which occurred when the patient abandoned therapy on her own volition (No. 17).

The 7 patients who were given combined therapy but who had responded to hexamethonium alone, obtained an additional reduction in blood pressure or were better stabilized when Apresoline was added. However, therapy had to be interrupted in 2 patients because of palpitations and tachycardia in the one and persistent headaches in the second. Of the 11 patients who had previously failed to respond to hexamethonium alone, 4 (Nos. 14, 16, 40, 41) showed a good response to combined therapy. However, 7 of the 11 proved resistant, and showed no better response to combined therapy than to hexamethonium alone.

Discussion. PHARMACOLOGY. Therapeutic agents which are capable of lowering the blood pressure can be divided essentially into 3 groups according to their primary site of action; namely, (1) centrally acting (brain) drugs, such as veratrum extracts (Veriloid, Vergitryl); (2) ganglionic blocking drugs which block the transmission of impulses through the autonomic ganglia (hexamethonium); and (3) peripheral blocking agents (Regitine, Dibenzyline) which block the transmission of impulses from the sympathetic nervous system to the end organ. Hexamethonium falls into the ganglionic blocking group of drug. It, like tetraethylammonium, is somewhat exceptional from many ganglionic paralyzing agents in that it does not stimulate the ganglia prior to paralysis. It differs from tetraethylammonium in that the paralysis lasts longer

and the hypotensive effect is much less variable and more prolonged. Hexamethonium chloride is a polymethylene bistrimethyl ammonium salt which is composed of two ammonium radicals united by a chain of a varying number of methyl groups. The compound so formed is named according to the number of methyl groups in the chain. Thus, a compound with 6 methyl groups in the chain is called hexamethonium (C_6); and one with five methyl groups, pentamethonium (C_5). When the chain is increased to 10 methyl groups, the compound has a curare-like action and is being investigated in circumstances where a blockade of nervous impulses over the striated neuromyal junction is desirable. Paton and Zaimis[11] found that C_5 and C_6 produced ganglionic blockade of the autonomic nervous system. When hexamethonium produces ganglionic blockade it blocks the parasympathetic ganglia as well as the sympathetic ones. Most of the side effects associated with the reduction in blood pressure can be attributed to a mild carry-over of the curare-like effect (weakness and fatigue), parasympathetic ganglionic blockade (constipation, urinary retention, dry mouth, and anorexia), or excessive hypotension (dizziness and syncope) which is predominately orthostatic. The drug apparently blocks cardioaccelerator reflexes associated with acute reduction in blood pressure. Therefore, one does not see reflex tachycardia after hexamethonium as one sees it following blood pressure reduction by adrenergic blocking drugs and other means.

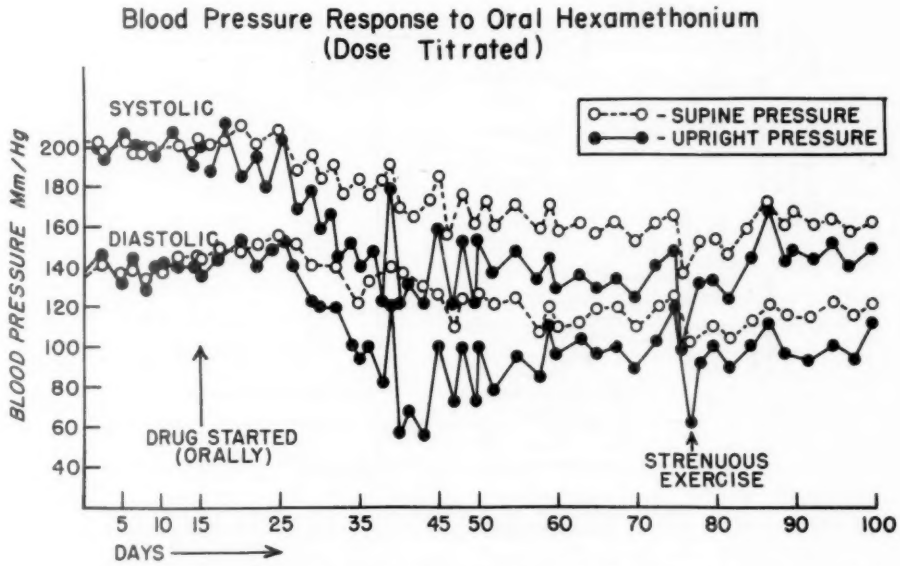

FIG. 1.—This is a graphic record of the supine and upright blood pressure during the control period, during the period of drug titration, and after reduction in the blood pressure. The two main problems with this therapeutic approach are obvious. These are: (1) the variability in blood pressure response; (2) the reduction in the blood pressure is predominantly orthostatic.

When the blood pressure is reduced, the cerebral vessels dilate and cerebral

blood flow and cerebral metabolism are maintained[2]. However, if the pressure is reduced excessively, cerebral blood flow goes down and disturbances in cerebral function follow[9]. This is particularly likely to occur in the upright position since reflexes responsible for adjusting peripheral vascular resistance, to compensate for changes in position, are also blocked by hexamethonium. Therefore, the blood pressure should always be taken both in the supine and upright positions when evaluating therapy with this type of drug (Fig. 1). It is important that the dose of hexamethonium be *regulated according to the upright blood pressure.*

Following acute blood pressure reduction with hexamethonium, there is an initial depression of renal function. However, glomerular filtration gradually returns to normal despite a maintained reduction in blood pressure provided the reduction is not excessive. Patients with renal damage respond qualitatively similarly to patients with normal kidneys but the readjustment is slower[10]. Occasional patients fail to completely readjust to a lowered blood pressure.

If readjustment is incomplete little concern need be exerted if the pretreatment renal function was relatively normal because of the wide margin of functional renal reserve. However, if renal function is markedly impaired, even small reductions in glomerular filtration may seriously decompensate the excretory capacity of the kidney. Therefore, in the presence of impaired renal function, the therapist must be alert to this possibility. When excessive reduction in blood pressure occurs,

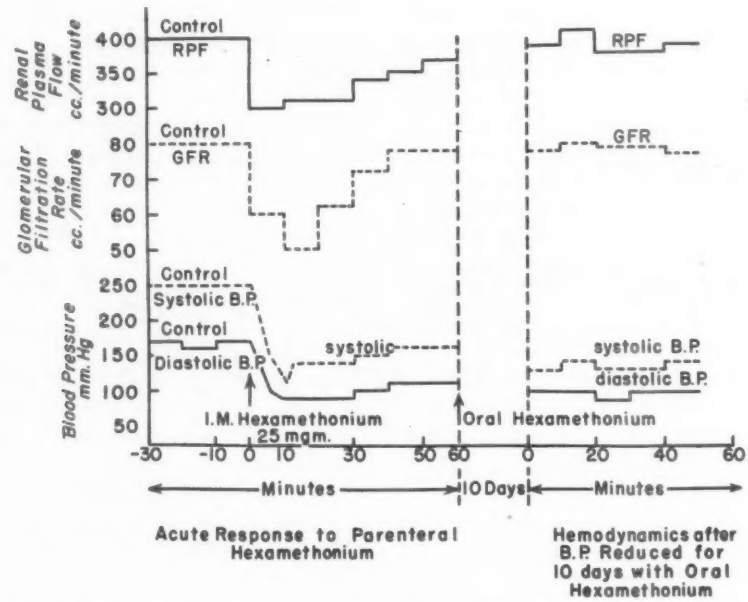

FIG. 2.—Acute and long term renal hemodynamic response to hexamethonium. Following parenteral administration, there was an initial depression of renal function but this rapidly returned toward normal despite a maintained reduction in systemic blood pressure. When the patient was placed on oral hexamethonium instead of the parenteral drug, the blood pressure remained reduced and renal hemodynamics were not altered.

norepinephrine infusion, or any good peripherally acting vasopressor agent, will quickly reverse the process and improve glomerular filtration towards normal since hexamethonium has no peripheral blocking action. Observations on glomerular filtration rate (inulin clearance) and renal plasma flow (para-aminohippurate clearance) before and after receiving hexamethonium for one month are presented in Table 5.

TABLE 5.—RENAL HEMODYNAMICS BEFORE AND AFTER REDUCTION IN BLOOD PRESSURE FOR ONE MONTH WITH ORALLY ADMINISTERED HEXAMETHONIUM CHLORIDE

Patient No.	GFR		RPF		Mean Blood Pressure	
	C	D	C	D	C	D
65-H	100	99	572	697	156	120
66-H	52	48	221	185	210	180
67-H	90	86	445	477	160	130
68-H	67	73	570	752	123	105

C—Control
D—One month after blood pressure reduction with hexamethonium.
GFR—Glomerular filtration rate, cc/minute.
RPF—Renal plasma flow, cc/minute.

* Mean blood pressure = diastolic pressure plus ⅓ of pulse pressure (supine).

Clinical. Most of the problems and complications resulting from prolonged hypertension arise in three vascular beds. These are the brain, the heart and coronary vessels, and the kidneys. The present studies confirm many previous observations that the cardiac and cerebral functions in patients with hypertension are improved by reducing the blood pressure. Hypertensive headaches were relieved in about three-fourths of the patients. None of the patients in the current study who maintained a reduction in blood pressure developed any cerebral complications. As the blood pressure is reduced, the cerebral vessels dilate[2] and thus maintain cerebral blood flow even in the presence of severe hypertension. This cerebral vaso-dilatation apparently helps to prevent thrombi. Certainly, it reduces the possibility of hemorrhages and small vessel bleeding. This was well demonstrated in the improvement and resolution of the retinal hemorrhages in numerous instances. If the pressure is reduced excessively, one might anticipate complications such as cerebral ischemia with thrombosis and paralytic phenomena. Cerebral ischemia as manifested by dizziness and occasional syncope was frequently seen in the upright position, particularly if the blood pressure was adjusted to normotensive levels in the supine position. However, cerebral thrombosis was not observed. One older patient developed transient weakness at a time that her blood pressure had declined excessively to 80 mm. Hg systolic and 50 mm. Hg diastolic in the upright position. The temporary paresis was probably a result of transient ischemia of the motor cortex. As soon as the patient lay down, all symptoms were relieved and full motor function returned.

The decrease in precordial pain and improvement of the anginal syndrome in many instances suggests that the ratio of coronary flow to oxygen and metabolite demand is improved. In only one instance was coronary pain precipitated by the reduction in blood pressure; whereas definite improvement in angina was noted in three-fourths of the patients who suffered with this complication. Apparently the reduction in work load on the heart compensates for any decrease in coronary blood flow, if this occurs as a result of the reduction in blood pressure. It also is quite possible that ganglionic blockade of the nerves to the heart inhibits any vasoconstrictor impulses traveling to the coronary vessels.

Reduction in blood pressure and its resultant decrease in work load on the heart was of definite benefit to the patients in heart failure. Definite symptomatic improvement occurred in about three-fourths of the patients.

TABLE 6.—COMPARISON OF BLOOD PRESSURE RESPONSE* OF HEXAMETHONIUM WITH OTHER HYPOTENSIVE DRUGS

	No. Pts. Treated	*Normotension***		*Decrease MBP 40 mm. Hg or more*		*Decrease MBP>30 mm. Hg but less than 40 mm.*		*MBP>20 mm. Hg but less than 30 mm.*		*Decrease MBP>20 mm. Hg*		*Long Term Follow-Up Continued Response****	
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Hexamethonium													
Group 1	16	5	31	10	63	2	13	1	6	13	81	10†††	63
Group 2	27	13	48	15	56	6	22	1	4	22	81	15†††	56
Group 3	15	10	67	1	7	7	47	4	27	12	80	10†††	67
Total	58	27	—	26	—	15	—	6	—	47	—	35	60
% of All Pts. Treated			47		45		26		10		81		
Dibenzyline	32	14	44	15	47	3	9	3	9	21	66	11‡	34†
Regitine	24	—	—	—	—	2	8	2	8	4	17	None‡	
Anatensol	31	1	3	1	3	3	10	2	6	6	19	2‡‡	6
Veriloid	30	2	7	6	20	2	7	7	23	15	50	6‡‡	20††
Apresoline	52	5	10	5	10	4	8	8	15	17	33	4‡‡	8

* Upright blood pressure.
** Blood pressure less than 150/100 in upright position.
*** Mean blood pressure reduced 20 mm. Hg or more or below 150/100 (normotensive).
† One patient previously controlled failed to return to clinic—calculated on basis of 31 patients.
†† Calculated on basis of 28 patients since 2 who originally responded failed to return.
††† Follow-up after 4 to 16 months.
‡ Follow-up after 3 to 6 months.
‡‡ Follow-up after 1 to 2 years.

A decrease in venous return pressure[3] with a subsequent reduction in cardiac dilatation and improved cardiac efficiency was probably a significant component of the beneficial results noted in patients with heart failure. These observations lead to the conclusion that if cerebral pathological changes, coronary artery disease, or cardiac failure exist either alone or in combination and if they are secondary to severe and prolonged hypertension, attempts to reduce the blood pressure should be undertaken. This is particularly true if renal function is not impaired. On the other hand if impairment of renal function dominates the clinical picture, caution must be exercised when reducing the blood pressure, since one may produce further impairment of renal excretory capacity. Although the damaged kidney responds to a reduction in blood pressure by vasodilatation in a relatively normal fashion this occurs more slowly[10] and is occasionally incomplete. Incomplete renal hemodynamic readjustment is more likely to occur if the blood pressure is reduced to absolute normotensive or hypotensive levels. In the presence of renal damage glomerular filtration is critical and small absolute changes may throw the patient into frank or progressive renal failure. This does not indicate that blood pressure reduction is not feasible in the presence of impaired renal function. It does indicate that when blood pressure reduction is undertaken it must be done with extreme caution and with constant evaluation of renal excretory function. Any tendency towards an increase in the blood urea nitrogen is a definite *contraindication* to further reduction in blood pressure. If the blood urea nitrogen cannot be determined repeatedly, hypotensive therapy should not be undertaken in patients exhibiting azotemia.

When hexamethonium is compared with some of the other current drugs which have been used under similar circumstances, the superiority of the former as a hypotensive agent is obvious. This is particularly true when long term follow-up is compared rather than initial responsiveness. When veratrum viride preparations such as Veriloid and Anatensol are administered by the oral route, the mean blood pressure can be reduced 20 mm. Hg or more in 20 to 50% of patients. However, in only a small number of patient (3 to 7%) can the pressure be reduced to levels approximating normal ranges (150/100 or less). Occasional nausea and vomiting will be experienced at some time in nearly all patients. This limits its usefulness over a long period of time and follow-up after one year indicates that 20% of the patients or less continue to obtain any reduction in blood pressure from the control observations.

The use of 1-hydrazinophthalazine is of limited usefulness when given alone, either orally or parenterally, due to the side effects, particularly the sympathomimetic effect on the heart with the resultant tachycardia and increased cardiac output. This is of serious concern in the presence of coronary artery disease wherein myocardial ischemia may develop as a result of the cardiac stimulant effect on a heart in which the coronary arteries are unable to deliver an adequate supply of blood to the myocardium. When the tachycardia is marked, the electrocardiogram shows T wave changes indicative of coronary insufficiency, presumably on the basis of the increased cardiac work[8]. If the sympathomimetic effect on the heart is previously blocked off by the use of ganglionic blockade, 1-hydrazinophthalazine is a valuable adjunct to the treatment of hypertension. Out of 18 patients who were given combined hexamethonium and 1-

hydrazinophthalazine therapy, 11 were previously proven to be resistant to hexamethonium, and 7 were proven responsive to hexamethonium, but the blood pressures either fluctuated unduly or the reduction in blood pressure was inadequate. In the latter group, all have shown greater stability or an additional reduction in blood pressure on combined therapy than on hexamethonium alone. The blood pressure was returned to normal limits in 6 out of the 7 patients (Table 4). However, it was necessary to discontinue this therapeutic program in 2 of the patients because of side reactions. Seven of the 11 patients who were unresponsive to hexamethonium alone also did not respond when Apresoline was added to the therapy. Two of these patients have died as a direct result of their hypertension. Four patients who were unresponsive to hexamethonium alone obtained a good response to combined therapy. These observations indicate that Apresoline has a place in the treatment of hypertension. In the authors' opinion, the place for Apresoline in the treatment of hypertension is in combination with hexamethonium or following surgical sympathectomy in patients who do not obtain an adequate reduction in blood pressure with either one of these procedures when used alone. This conclusion is reached because of the greater difficulty in regulating dosages on combined therapy, and the higher incidence of side reactions which includes headache, diarrhea, dyspnea, nausea, vomiting, and occasional paresthesias, most of these being due to the 1-hydrazinophthalazine.

Dibenzyline is the most effective peripheral acting adrenergic blocking agent. If the patients continue taking the drug, a reduction in blood pressure can usually be maintained[5]. Sixty-six per cent of the patients obtained an initial reduction in mean blood pressure of 20 mm. Hg or more as compared to 81% in the case of hexamethonium. The percentage of patients in whom the upright blood pressure returned to normotensive levels was about equivalent with both drugs. However, patients receiving Dibenzyline frequently develop reflex tachycardia and palpitations as the blood pressure decreases since the sympathetic nerves to the heart are not blocked. In addition, patients receiving this drug "just feel bad" without being able to identify the complaint, probably a cerebral effect. These side effects are limiting factors in most instances and are reflected in the reduced number of patients who benefit from the drug after 3 months or more of treatment (Table 6). Only 34% of patients continued to take Dibenzyline after 3 months. The tachycardia is particularly difficult to control, the presence of which is probably not warranted in the treatment of hypertension on a long term basis. It has been known for some time that the adrenergic blocking drugs do not block the effect of the sympathetic nervous system on the heart. By contrast, the ganglionic blocking drugs apparently block the sympathetic impulses before they reach the heart. Therefore, hypotensive reflex tachycardia is not a factor with hexamethonium. This makes hexamethonium more satisfactory in this respect and is an important reason why long term therapy with this drug is so much more successful than is the case with Dibenzyline.

Summary and Conclusions. 1. The results obtained with hexamethonium chloride administered orally for the treatment of 58 patients with hypertension have been summarized. The patients in this study have been treated as outpatients and followed from 4 to 16 months following the induction of therapy. The conditions of patient

care have closely paralleled those which are met in a general office practice. Therefore, the results obtained in the present study should closely parallel those obtained in a general office practice provided that the therapist understands the pharmacodynamics of the drug and pays strict attention to the regulation (titration procedure) of a dosage schedule which is an individual problem in each patient. There is no set dose and the dose must be titrated in each patient in order to establish maximum blood pressure regulation. If this is not done, excessive hypotension and serious complications may result.

2. Hexamethonium chloride when administered orally is an effective agent for reducing the blood pressure. Of 58 patients treated, all but 11 responded with a significant (mean blood pressure decreased more than 20 mm. Hg) reduction in blood pressure and in about one-half of the patients the upright blood pressure returned to normal limits. The amount of drug required was only slightly greater in the patients with diastolic blood pressures above 140 mm. Hg as compared to those with pressures less than 120 but more than 100. No difference could be detected between the unresponders and those who responded except that patients with severe hypertension complicated by cardiac failure and moderate to marked renal disease seemed to be particularly resistant to therapy.

3. Cerebrovascular disease and heart disease (cardiac failure, angina pectoris) seem to be particularly benefited by a reduction in blood pressure with hexamethonium. The renal vessels dilate and maintain renal blood flow and glomerular filtration rate about equal to the control observations in most instances. Damaged kidneys respond in essentially the same way that normal ones do. Therefore, impaired renal function (even if uremia is present) is not a contraindication to hypotensive therapy. However, in the presence of renal damage, glomerular filtration is critical and small changes may precipitate frank and progressive renal failure. This demands that in the presence of moderate to marked impairment of renal function, reduction in blood pressure must be undertaken with extreme caution and with constant evaluation of renal excretory function. Any tendency toward an increase in blood urea nitrogen is a contraindication to further reduction in blood pressure. If close supervision and repeated evaluation of the blood urea nitrogen is not feasible, then hypotensive drug therapy with hexamethonium is definitely contraindicated.

4. The combined administration of 1-hydrazinophthalazine (Apresoline) and hexamethonium further improved the blood pressure regulation in 11 of 18 patients in whom adequate control was not obtained with hexamethonium alone. Apresoline is indicated as an adjunctive therapeutic agent in those patients who do not obtain adequate reduction in blood pressure to hexamethonium alone.

5. Hexamethonium chloride was superior to other orally active hypotensive agents used in the same clinic under similar circumstances. Dibenzyline produced somewhat comparable results initially but proved to be inferior to hexamethonium as a long term therapeutic agent. This was due largely to the inability for this drug to block off the sympathetic innervation to the heart resulting in reflex tachycardia following blood pressure reduction. The tachycardia was particularly marked in the upright position.

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THE INACTIVATION OF ANTIBIOTICS BY CATION EXCHANGE RESINS

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Cation exchange resins are being used in edema states as a means of removing sodium from the body. However, since these resins are not individually selective, they combine with any substance which has a positive charge or which is amphoteric[3]. In addition to cations they will absorb such materials as thiamin, riboflavin and alkaloids (quinine, atropine, scopolamine).

The problem of whether other orally administered medicaments would be inactivated by these exchangers arose during the management of patients with edema[2]. A chronic rheumatic cardiac patient with marked congestive heart failure was being treated successfully with an exchange resin when she developed atypical pneumonitis. Since it was not known whether the oral antibiotics would be effective if used simultaneously with the resins, the problem was investigated.

Method. A modified filter paper strip method was used[1,4] to determine growth inhibition of four known organisms by the common antibiotics and to note any differences when a cation exchange resin was added.

The organisms were *M. citreus*, *Streptococcus* A_6A_h, *E. coli* and a paracolon bacillus. The concentrations per cc. of the standard antibiotic solutions were: penicillin 50 units, chloramphenicol 250 mcg., dihydrostreptomycin 500 mcg., terramycin 200 mcg., and aureomycin 100 mcg.

Broth cultures of the organisms were standardized with the Coleman Jr. spectrophotometer and blood plates prepared from these. Filter paper strips, 7 x 1 cm., were immersed in the antibiotic solutions and allowed to drain for 5 seconds. These strips were then placed in the center of the blood plates and incubated overnight. The zone of inhibition of bacterial growth was then measured.

Two grams of a cation exchange resin* were added to 20 cc. of the standard antibiotic solutions. These mixtures were agitated on a Kahn shaker for 5 minutes. Some of the filter paper strips were then immersed immediately and plated as above, while other filter paper strips were immersed after the mixtures had been allowed to stand for 5 hours. The zones of inhibition were measured after overnight incubation. In the case of chloramphenicol plus the resin, a mixture 24-days old was also tested.

A control experiment was performed using a similar concentration of resin in sterile, distilled water. The pH values of the resin and antibiotic mixtures were determined. Turbidimetric tube dilution methods could not be utilized because of the turbidity produced by the resin.

Results. The resin alone did not inhibit the growth of any of the organisms tested. Table 1 summarizes the results obtained with *M. citreus* (Gram-positive) and *E. coli* (Gram-negative). Other organisms, Streptococcus A_6A_h and *Paracolon B.*, were used throughout the experiment with similar find-

* Katonium, an ammonium sulfonated polystyrene type resin, was supplied by Winthrop-Stearns Inc., New York.

ings. In each instance, when the antibiotic was used alone, a significant zone of inhibition was obtained.

When penicillin or chloramphenicol was combined with the cation exchange resin, the zone of inhibition was the same as when the antibiotic was used alone. This indicates that the resin did not inactivate either of these antibiotics. The results with chloramphenicol were identical when the mixture was used immediately or allowed to stand for as long as 24 days prior to its use.

broth and *M. citreus* to 6.25 for the mixture of resin, broth, *Streptococcus* A_6A_k and penicillin.

Discussion. These findings indicate that dihydrostreptomycin, terramycin and aureomycin are significantly inactivated by cation exchange resins. Penicillin and chloramphenicol are not inhibited by these exchangers. It was subsequently learned that the commercial methods of concentrating streptomycin involve the use of cation exchange resins.

TABLE 1.—BACTERIAL GROWTH WITH RESIN-ANTIBIOTIC MIXTURES

Resin-Antibiotic	*Gram-positive (M. citreus)*	*Gram-negative (E. coli.)*
Resin alone	0*	0*
Penicillin alone	35–40	—
Penicillin + resin		
Immediate	35–40	—
5 hours	35–40	—
Chloramphenicol alone	8–15	5–9
Chloramphenicol + resin		
Immediate	10–15	5–9
5 hours	8–13	5–9
24 days	8–15	5–9
Dihydrostreptomycin alone	4–6	5–7
Dihydrostreptomycin + resin		
Immediate	0	0
Terramycin alone	9	9
Terramycin + resin		
Immediate	7–9	1–3
5 hours	0–1	0
Aureomycin alone	9	5
Aureomycin + resin		
Immediate	5–8	0
5 hours	0–1	0

* Zone of inhibition of growth in mm.

Dihydrostreptomycin, when combined with the resin, lost its antibacterial activity immediately for both Gram-positive and Gram-negative organisms.

Terramycin (both crystalline and HCl) and aureomycin when combined with the resin were inactivated within 5 hours. In the case of the Gram-negative organisms the inactivation occurred immediately.

The pH values varied within the limits of 6.5 for the mixture of resin,

Any pH variations attributable to the resin could not have been responsible for the results obtained because the resin alone did not produce similar changes. In addition, the measured pH values were within a relatively narrow range.

It would seem then that antibiotic substances which can be absorbed by cation exchange resins may lose their antibacterial activity if they first come in contact with the resins. On the other hand, the antibiotics which are not

absorbable by the resins may not be so inhibited.

Summary. These *in vitro* studies show that the antibacterial properties of penicillin and chloramphenicol are not inhibited by the cation exchange resins. The antibacterial activities of dihydrostreptomycin, terramycin and aureomycin are suppressed by these resins.

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POLYMYXIN B IN CHRONIC PYELONEPHRITIS: OBSERVATIONS ON THE SAFETY OF THE DRUG AND ON ITS INFLUENCE ON THE RENAL INFECTION*

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SINCE the studies of Weiss and Parker[14] it is generally accepted that the seat of infection and inflammation in pyelonephritis is predominantly in the interstitial tissue of the kidney and not primarily within the tubular and ductal system. One even observes instances of interstitial infection and inflammation without any intratubular involvement. This localization of inflammation and infection has an important bearing on the frequent discrepancy between urinary findings and symptomatology.

All too often the treatment of urinary tract infection is directed at a sterilization of the urine, rather than at eradication of the focus of infection in the renal parenchyma. Yet a consideration of the natural history of pyelonephritis such as developed by Longcope and Winkenwerder[9], and Birchall[1] points to the urgent necessity of dealing with the infection in the renal interstitial tissue which threatens the integrity of renal structure and function, rather than treat temporary, incidental symptoms often referable to the lower urinary tract.

The great majority of chronic urinary tract infections are caused by Gram-negative bacteria. The commonly employed antimicrobial substances effective against such microorganisms, for example, sulfonamides, aureomycin, chloramphenicol, and terramycin are principally bacteriostatic agents. They are highly effective in many instances in sterilizing the urine, and concomitantly alleviating the symptoms of inflammation. However, they are probably as ineffective in eradicating interstitial tissue infection in the renal parenchyma as they are ineffective in curing subacute bacterial endocarditis[2,7].

In order to be successful in the sterilization of the renal parenchyma a drug should be highly bactericidal against Gram-negative organisms. It should penetrate and diffuse well, and should be sufficiently non-toxic to be administered for a long enough time to permit eradication of all bacteria; not merely to cause suppression. Polymyxin B is a drug fulfilling at least the first of these requirements. It is strongly bactericidal against a majority of Gram-negative bacteria[6,13] and is capable of sterilizing the urine temporarily in chronic urinary tract infection due to susceptible bacteria[6,11,12].

* Supported by a grant-in-aid from Burroughs Wellcome and Co, Tuckahoe, New York.

Objections to its use originate in suspicions of nephrotoxicity and from the known unpleasant, if harmless, neurotoxic side effects[6]. Experimental work has indicated that the chronic nephrotoxicity of Polymyxin B is slight, whereas that of several other members of the family of Polymyxins is considerable[8]. Earlier clinical investigation had suggested that Polymyxin B could be safely administered to persons with chronic pyelonephritis in a dose of 2 mg./kg./day for 7 days. The present investigation was undertaken to establish the possibility of prolonging the treatment with Polymyxin B beyond one week, even in patients with renal insufficiency, with the idea of eradicating the infection in the interstitial tissue of the kidney.

Materials and Methods. Thirteen patients with pyelonephritis of long standing were treated with Polymyxin B. All were known to have had positive urine cultures for a number of years. Seven of these patients had essentially normal renal function judged by endogenous creatinine clearance*, phenolsulfonphthalein excretion test, concentrating ability, blood nonprotein nitrogen, and serum creatinine concentration. Notwithstanding normalcy of these tests some had moderate proteinuria as indicated in Table 2, and all had abnormal numbers of white and red cells in the urine. Six other patients were in various degrees of renal failure indicated by creatinine clearances which were slightly reduced, or greatly reduced, with other accompanying signs of renal insufficiency usually passing under the term uremia. Several had hypertension as a complication; none were in frank congestive heart failure.

Two additional patients were included in the series although they did not have clearly defined chronic pyelonephritis. One (EMB) had intermittent evidence of urinary tract infection, with good kidney function, and was treated with Polymyxin B for an incapacitating respiratory infection with *Pseudomonas aeruginosa*. The second patient (CC) developed ureteral obstruction by a squamous carcinoma of the vulva which had invaded the pelvis. She was treated with Polymyxin B in an attempt to control the infection of the urinary tract above the obstruction. No other patient had manifest obstruction in the lower urinary tract.

* Normal 72 to 140/cc./min. (4)

Aerosporin brand Polymyxin B (Lots W 345 and W 985) was supplied by Dr. D. S. Searle, Burroughs Wellcome and Co., in vials concontaining the equivalent of 50 mg. of the pure drug in the form of material of approximately 75% purity. For injection the material was dissolved in 1 or 2 cc. saline per vial. Sufficient procaine hydrochloride to give a final concentration of ¼% was added for intramuscular administration. Three patients received the drug in intravenous infusions of 5% dextrose in water (50 to 100 mg. of Polymyxin B suspended in 250 cc. of 5% dextrose). Samples of blood and urine were obtained from a number of patients at intervals after injection of the drug, for determination of Polymyxin B levels. These were carried out by a tube-dilution method, using for assay a Shigella organism which was completely inhibited by 0.05 microgram/cc. of Polymyxin B.

During the period of study, before, during and after treatment the following tests were performed on most patients every 4 or 5 days: blood nonprotein nitrogen, serum creatinine, endogenous creatinine clearance[4], quantitative protein and Addis count of urine, and quantitative urine cultures. Urinary protein was quantitated on 12-hour urine aliquots by the method of Hiller, Greif, and Beckman[3]. Creatinine of serum and urine was determined by J. H. Peters' modification of Folin and Wu's method[10]. Patients with severe renal insufficiency were not dehydrated for the Addis count. In addition all patients had complete blood counts, before and after treatment and serum electrolyte determinations when indicated.

Results. The effects of Polymyxin B administration on renal function, shown in Table 1, appear to depend largely on the patient's renal status prior to therapy. The results are, therefore, discussed and tabulated by groups in relation to whether the patients initially (before treatment) had normal or impaired function.

Eight patients with essentially normal renal function received from 1250 to 2375 mg. of drug intramuscularly in 9 to 14 days, with a daily dose range of 1.7 to 2.2 mg./kg. All these individuals experienced some local pain with the injections. followed sometimes by sciatic pain. Some also had flushing of the face, increasing dizzi-

TABLE 1.—RENAL FUNCTION IN POLYMYXIN B THERAPY

		Treatment		Before treatment			During treatment			After treatment		
Patient	*Creatinine clearance*	*Number of days treated*	*Total amount Polymyxin mg.*	*NPN mg./100 cc.*	*Serum Creatinine mg./100 cc.*	*Creatinine clearance cc./min.*	*NPN* mg./100 cc.*	*Serum* Creatinine mg./100 cc.*	*Creatinine† clearance cc./min.*	*NPN mg./100 cc.*	*Serum Creatinine mg./100 cc.*	*Creatinine clearance cc./min.*
V. R.[1]		13	1450	28	0.9	86.3	30	1.0	78.8	27	0.8	85.5
E. C.[1]	Normal	13	1700	22	0.9	76.8	30	1.1	78.7	20	1.0	81.1
E. M. B.[1]	Creatinine	13	1950	40	0.7	88.8	35	1.0	77.2	32	1.0	72.1
L. W.	clearance	13	2050	40	0.6	164.0	35	0.9	85.0	32	1.3	70.0
B. C.	Range	14	1400	40	0.9	84.8	35	1.1	74.0	32	0.9	96.6
B. R.	72–140	12	1500	34	0.8	93.0	32	1.0	108.0	38	0.7	121.0
A. M.		14	2375	—	0.8	108.0	—	1.3	94.5	—	1.2	144.0
M. H.		9	1250	32	0.8	130.0				29	0.9	69.0
A. H.		6	700	35	1.2	65.0	41	1.1	35.0	39	1.9	37.0
A. E.	Impaired	8	720	—	1.0	65.0	—	1.2	68.0	—	1.3	60.0
H. L.		10	1250	50	3.6	27.2	66	4.7	16.4	58	3.7	17.3
M. E. H.	Creatinine	12	1200	—	3.7	16.1	—	5.3	8.6	—	4.1	27.6
G. H. B.		10	475	102	13.0	4.5	100	13.2	—	104	14.0	2.1
A. T.	clearance	6	450	48	2.8	29.0	—	—	—	72	3.0	21.2
C. C.		9	1000	46	2.0	44.4	76	—	—	72	4.1	10.3

[1] Reference 5

[2] Normal serum creatinine values 0.6 to 1.6 mg./100 cc. (4)

* Highest values

† Lowest values

TABLE 2.—ADDIS COUNTS IN POLYMYXIN B THERAPY

	Before Treatment				*During Treatment*				*After Treatment*			
Patient	*Protein gm./24 hrs.*	*RBC × 10⁶*	*WBC × 10⁶*	*Casts × 10³*	*Protein gm./24 hrs.*	*RBC × 10⁶*	*WBC × 10⁶*	*Casts × 10³*	*Protein gm./24 hrs.*	*RBC × 10⁶*	*WBC × 10⁶*	*Casts × 10³*
V. R.	0	2	31	0	0.2	5	14	0	0	3	7	0
E. C.	0	16	65	0	0	19	84	0	0	10	52	0
E. M. B.	0.3	1	4	0	2.0	2	14	100	0	0.5	2	25
L. W.	0	1	56	0	0.5	2	41	0	0.2	6	60	0
B. C.	0	0	4	0	0	0.3	5	0	0	0.05	0.5	0
B. R.	0.1	2	32	0	0.36	1	0.75	0	0	0	5	25
A. M.	0.6	12	386	0	0.4	5	593	275	1.2	488	2100	2000
M. H.	0.9	10	461	0	0.9	185	195	50	0.8	192	64	0
A. H.	0.1	5	92	50	0	0	20	50				
A. E.	0	4	120	10					0	9	144	16
H. L.	3.0	69	768	0	2.2	556	417	0	1.6	26	1726	0
M. E. N.	6.0	47	90	75	3.5	4	2	0	2.7	3	5	0
G. H. B.	2.0	10	1000	0	2.7	700	100	0	2.2	100	100	0
A. T.	1.0	39	1131	0					1.2	10	53	50

ness, light headedness or headache, perioral paresthesias, peripheral paresthesias and sometimes sensation of coldness and the other signs of neurotoxicity associated with Polymyxin B described earlier[5,6]. Inconstantly there was severe headache requiring codeine, and sometimes there was moderate pruritus. All these side actions disappeared within 48 hours after the drug had been discontinued.

In these 8 individuals the administration of Polymyxin B in the dosage range stated above did not result in demonstrable or persistent impairment of renal function (Table 1). Shortly after the beginning of drug administration the creatinine clearance values tended to rise temporarily, perhaps associated with the vasodilatation evident in other parts of the body[8]. Soon, however, the values returned to their pre-treatment level and remained there for weeks and months after administration of the drug. Thus damage to renal function did not appear to be induced by the dosage range employed in persons with initial good function. The studies of proteinuria and urinary sediment in this group likewise did not suggest the occurrence of renal damage (Table 2). In several individuals who had measurable proteinuria before treatment, the transient increase during therapy failed to persist. While all these patients had red and white blood cells in their pre-treatment urine, there was no uniformly consistent change associated with treatment. Casts appeared in 4 individuals in the course of drug administration, but disappeared again within 1 to 2 months. It may be summarized then that in 8 individuals with urinary tract infection and good kidney function administration of 1.7 to 2.2 mg./kg./day Polymyxin B for 9 to 14 days did not give evidence of significant nephrotoxic action.

The 7 cases comprising the second group had evidence of impaired renal function. It had been discovered in earlier work that persons who retain nitrogen also tend to accumulate Polymyxin B and excrete it more slowly than those with normal kidney function[6]. Consequently the dosage range of Polymyxin B was kept between 0.8 and 1.3 mg./kg./day for from 6 to 12 days. Even with this lower dosage the side effects were much more marked than in the first group, particularly dizziness and headache. Three patients in this group received part, or all of the drug intravenously by slow drip (A.H., H.L., C.C.). The drug was well tolerated by this route which avoided the troublesome local pain after intramuscular injection. Other side effects appeared comparable in intensity to that following the intramuscularly injected similar dosage.

In 4 patients of this group some nephrotoxic action could be attributed to the drug, evidenced by a further depression of creatinine clearance and a rise in nonprotein nitrogen and/or creatinine. While this was usually a transient phenomenon it gave rise to concern and at times led to discontinuance of treatment with Polymyxin. This depression of renal excretory function is not mirrored in the Addis counts on this group of patients, inasmuch as there was no uniform trend in proteinuria or sediment. It appears from these data that notwithstanding reduced dosage, prolonged administration of Polymyxin B may have nephrotoxic effects in individuals with grossly impaired renal function. It follows that in such patients this drug should be used only when adequate laboratory facilities are available for appraisal of kidney function. The blood picture was not influenced by the drug in any patient.

During treatment with Polymyxin B susceptible bacteria in the urine were

usually suppressed, but *Proteus*, Gram-positive bacteria, and some *Pseudomonas* strains were not affected (Table 3). In patients whose cultures became negative during treatment bacteria reappeared in from 1 to 4 months, unless continuous suppressive therapy was administered. The bacteriological relapse with the same organism as originally present suggests that the focus of infection in the interstitial tissue was suppressed but not eradicated. The blood level of Polymyxin B reached as high as 15 micrograms/cc. in some patients, and during the treatment period did not fall below 1 microgram/cc. Urine levels of the drug could not be measured regularly. The failure to eradicate the infection must be attributed to shortness of treatment period, and perhaps poor penetration of the drug into the infected area rather than generally inadequate tissue levels. The following brief case summaries illustrate representative experiences.

TABLE 3.—EFFECT OF TREATMENT WITH POLYMYXIN B ON THE RESULTS OF URINE CULTURES
Number of bacteria per cubic centimeter of urine

Patient	*Pre-treatment culture*	*During treatment*	*Post-treatment cultures*		
			1 week	*1 month*	*2–4 months*
V. R.	*A. aerogenes* 10^5	0	0	10^7	—‡
E. C.	*Proteus* 10^4	10^4	5×10^4	—	—
	E. coli 5×10^4	0	0		
L. W.	*E. coli* 10^7	0	0	10^6	—
	Ps. aeruginosa 10^2	5×10^2	10^2	10^2	—
B. C.	*E. coli* 3×10^6	0	0	0	10^7
B. R.	*E. coli* 10^8	0	0	5×10^7	10^7
A. M.	*Ps. aeruginosa* 5×10^3	5×10^3	5×10^4	10^7	10^6
M. H.	*E. coli* 10^7	0	0*	0*	0*
A. H.	*Pseudomonas* 10^8	0	0	—	—
A. E.	*E. coli* 10^9	—	10^9	—	—
H. L.	*Ps. aeruginosa* 10^7	10^5	10^8	—	—
M. E. H.	*E. coli* 10^9	0	0†	0†	0†
G. H. B.	*E. coli* 10^7	0	0	0	—
	Ps. aeruginosa 10^3	10^2	10^1	10^3	
	Strep. virid.	10^5	10^3	0	
A. T.	*E. coli* 10^7	10^4	0*	0*	0*
	Proteus 5×10^1	10^4	0	0	0
	Strep. virid. 5×10^3	10^5	10^2	0	10^1
C. C.	*Ps. aeruginosa* 10^5	0	0	Pt. expired	

* At end of Polymyxin B therapy placed on suppressive therapy with sulfadiazine 0.065 gm. 4 times daily.
† At end of Polymyxin B therapy placed on suppressive therapy with Mandelamine 0.25 gm. 4 times daily.
‡ No culture obtained.

Mrs. B.R., a 33-year-old housewife, had suffered from pyelonephritis 8 years. Shortly after her marriage 8 years ago the patient developed an attack of dysuria, frequency, nocturia and pyuria which subsided with sulfonamide therapy, but recurred at intervals with occasional bachache and hematuria. Five years ago she had a normal pregnancy and delivery. Urine from both kidneys uniformly grew *E. coli* for 4 years. Repeated urological investigations revealed no significant anatomical abnormality. Past chemotherapy included courses of sulfonamides, mandelamine, chloramphenicol and aureomycin, without definite or lasting effect on the infection. For over 1¼ years ureteral dilatations and irrigation with 2% silver nitrate were carried out. A culture on 8 November revealed 2.5 million *E. coli*/cc of urine.

Physical examination was essentially normal. BP:115/76. Examination of the blood was within normal limits. Other laboratory data are seen in Tables 1, 2 and 3. From 10 November, 1951 to 22 November the patient received daily intramuscular injections of Polymyxin B with procaine 2.2 mg./kg./day, to a total amount of 1500 mg. Ureteral catheterization carried out on 16 November, showed no obstruction, and cultures from both kidneys were sterile. During treatment the patient had only minor neurotoxic symptoms but suffered from severe local and radiating pain at the site of injection.

Urine cultures on 16 October, 23 October and 6 November, 1951, were sterile, but on 14 November and 26 December *E. coli* was present again, about 10 to 50 million per cc. The patient remained asymptomatic. With the physician's permission the patient became pregnant again, and went through an un-

eventful course except for two flare-ups of urinary tract infection which required short courses of chloramphenicol. On 17 August, 1952, the patient was delivered of a healthy child at term. Follow-up urine cultures on 20 September and 22 November, 1952, were sterile

Mrs. A.T., a 44-year-old registered nurse, had suffered from recurrent pyelonephritis since 1947. About 1949 she began to have attacks of severe right flank pain with anorexia, frequent nausea, vomiting, low grade fever and pyuria. Since that time she lost 23 pounds in weight. She had 3 episodes of uremia during which her nonprotein nitrogen rose to 90 mg./100 cc. or more and her blood pressure to 200/100. Urine cultures showed always a predominance of *E. coli*. Various courses of treatment including sodium acid phosphate and Urotropin, Gantrisin, penicillin, terramycin and streptomycin failed to eradicate her infection.

Physical examination showed a thin woman, not obviously ill, with blood pressure 165/95 without cardiac enlargement. Eyeground changes corresponding to Keith Wagener stage 2. Tenderness over the lower pole of the right kidney. Laboratory: Hemoglobin, 13.2 gm., leukocytes 3,700, serum creatinine 2.8, phenolsulfonephthalein 20% excreted in 2 hours. (See tables for other data.)

From July 8 to July 12, 1952, the patient received intramuscular injections of Polymyxin B, 25 or 50 mg. every 12 hours, to a total of 450 mg., or an average of 1.1 mg./kg./day. In addition to marked local pain the patient developed severe pruritus relieved little by antihistaminics, slight neurotoxic symptoms, anorexia and some depression. When Polymyxin B was discontinued she made a rapid recovery. Urine cultures were negative on discharge. Since that time the patient has been taking sulfadiazine 65 mg. 4 times daily and her urine cultures have remained negative. On 13 November, 1952, her serum creatinine was 2.6 mg./100 cc., her urinary protein output had decreased to 0.5 gm./24 hrs. and the pus cells in the urine to 10 million per 24 hours, and there were no bacteria in the urine.

Summary and Conclusions. Fifteen individuals were treated with Polymyxin B in order to evaluate the nephrotoxicity of the drug and its ability to eradicate infection in the interstitial tissue of the kidney. Eight of these had good kidney function as measured by normal endogenous creatinine clearance tests. In them the administration of 1.7 to 2.2 mg./kg./day of Polymyxin B for 9 to 14 days was not nephrotoxic.

The remaining 7 individuals had various degrees of impairment of kidney function, and were therefore treated with smaller amounts (0.8 to 1.3 mg./kg./day) of Polymyxin B. In 4 of these patients there was evidence of at least transient depression in creatinine clearance and of nitrogen retention. Thus the manifestation of nephrotoxicity of Polymyxin B appears to depend on the status of pre-existing kidney function. While prolonged treatment with this drug in full dosage appears safe in persons with good renal function, caution is necessary in cases of incipient, or manifest renal insufficiency.

In the time-dose schedule used in this experiment Polymyxin B did not regularly succeed in eradicating the infection in the renal parenchyma, even when it was due to drug-sensitive micro-organisms. It is uncertain whether more protracted therapy might accomplish the aim. Several patients maintained negative urine cultures for many months, when therapy with Polymyxin B was followed by small doses of sulfonamides.

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TETRAZOLIUM AS AN AID TO THE STUDY OF TUBERCLE BACILLI*†

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This paper represents a story of a new application of a substance which has reposed for a long time inactive upon the chemists' shelves. About a decade ago this substance, a colorless dye (2, 3, 5 triphenyltetrazolium chloride), was observed to undergo reduction in the presence of living cells to form an easily detectable red compound (red formazan). At this time botanists and agriculturists learned of the change in color of this dye when exposed to the living portion of cells, and they used it commercially to determine the percentage of viability in seed. These efforts indicated that certain types of living bacteria also effect the reduction, but little definitive work had been done in the field of bacteriology in respect to determining viability by use of this dye[6,8-10,12,13].

The scheme seemed to fit in well with a study that is being carried on at the North Carolina Sanatorium under a grant from the National Tuberculosis Association on a comparison between BCG and R_1. This latter, as many know, is a strain of tubercle bacillus of low virulence used extensively in this country for study of allergy, resistance and immunity to tuberculosis. BCG is distributed for vaccination throughout the country but, as dispensed to date, it is administered with little knowledge concerning the viability of the bacilli in suspension.

Method. Acid-fast bacilli can be harvested, washed, treated with tetrazolium for 2 hours in an incubator, during which time the living cells reduce the dye to red formazan which is extracted with acetone (Merck). This material is then centrifugalized, the supernatant fluid decanted, transferred to a monochromatic colorimeter and read for percentage transmission, which indicates the percentage of viable bacilli present[14]. In order to investigate the probable value of this tetrazolium salt as a viability test, approximately 20 mg. per cc. of 8-day cultures of tubercle bacilli (BCG and R_1), grown in Dubos'[5] Tween 80** medium with bovine albumin were used and were made into vaccines with Dubos' basal medium as a diluent. One-half of the resulting suspension was killed by flowing steam. The other half was maintained as a "live" vaccine. Dilutions were made using "live" vaccine in concentrations varying from 20 mg. to 0 mg. with corresponding numbers of dead bacilli to give a final concentration of 20 mg. per cc. and a volume sufficient for removal of 1 cc. for colony counts[13] and 1 cc. for tetrazolium reduction. The suspension for reduction studies was washed in order to remove the residual enzyme system which may be retained after death of the bacilli. This residual may reduce the tetrazolium. To each tube was added 1 cc. of 0.25% solution of 2, 3, 5 triphenyltetrazolium chloride contained in Dubos' basal medium with 0.5% glucose,

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† This study was made possible by a grant from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association.

** Tween 80 is the proprietary name for polyonyethylene derivative of Sorbiton mono-oleate, obtained from the Atlas Powder Company, Wilmington, Delaware.

0.02% Tween 80 and the pH adjusted to 7.2. This was incubated for 2 hours at 37½° C.

Results. It is observed in Fig. 1 that as the concentration of viable cells decreases, so does the extent of reduction, exemplified by the lessening of the color produced by the red formazan. At this stage the color is bound in the bacilli. There is a gradual variation in the extent of color from a fairly deep red in the tube containing all living bacilli to a colorless tube at the other end of the chain containing all killed bacilli.

This viability test has certain practical applications of value in the laboratory such as possible streptomycin sensitivity testing[15]. It can be applied to the standardization of doses for animal inoculation and enhancement of colony counting and photogenicity of cultures as described below.

1. STANDARD INOCULA: This test enables one to inoculate animals with comparable and standard doses. One hundred guinea pigs were inoculated with approximately equal numbers of viable bacilli (1.0 mg.). Results from such inoculation should be comparable if the strains are equal. The study further compared strains on two bases: (a) the titer of cord formation in culture; and (b) the duration of allergy produced by several strains when inoculated into guinea pigs. Such comparative observations are made possible by standard doses determined by use of this tetrazolium salt.

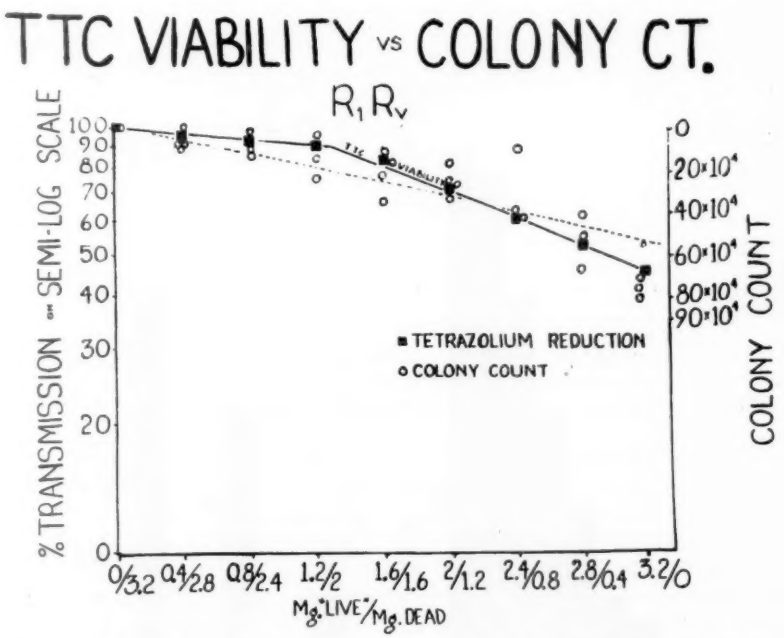

FIG. 1.—The reduction of 2, 3, 5 triphenyltetrazolium chloride to red formazan by the biologic activity of low concentrations (concentrations of 0 to 3.2 mg. per cc. were nephelometrically standardized) of living and dead tubercle bacilli (R_1 R_V), as indicated by percentage transmission. Lower transmission reading is due to less dilution of dye before reading. The trend of colony counts is plotted on regular graph paper.*

* Colony counts have been made repeatedly from various dilutions of the suspension mentioned above and compared with this viability test. This has been sufficient to indicate the complete reliability of the latter (Figure 1).

This is not a paper to discuss cord formation of tubercle bacilli, except insofar as standard doses of bacillary strains that vary markedly in the end point of cord formation vary significantly in ability to establish lasting infection when doses are predetermined by this viability test.

In liquid medium rich with human albumin fraction and plasma, various strains of tubercle bacilli grow to form serpentine cords. Some do not. Tween 80 when added to medium causes micro-organisms to disperse, depending upon the degree of virulence and, obviously, on the proportion of Tween 80 which is added. On this basis, as indicated in Fig. 2, three strains of BCG show marked differences as to the point in concentration of Tween 80 at which cords disperse: in one strain (No. 6 in Fig. 2) this takes place at a concentration of 0.010; in No. 7 at 0.030; and No. 8 at 0.050. R_1 (No. 9) and virulent strains (Nos. 10 and 11) retain cord formation at still higher concentrations. It is obvious from the Figure (right side) that those strains having slight ability to form cords in the presence of a dispersing agent establish infection in guinea pigs (when standard doses are used: 1.0 mg. viable bacilli in this instance) which is of comparatively short duration[14].

2. Enhancement of colony counting and photogenicity of cultures. The detection of colonies and their photogenicity are enhanced greatly if

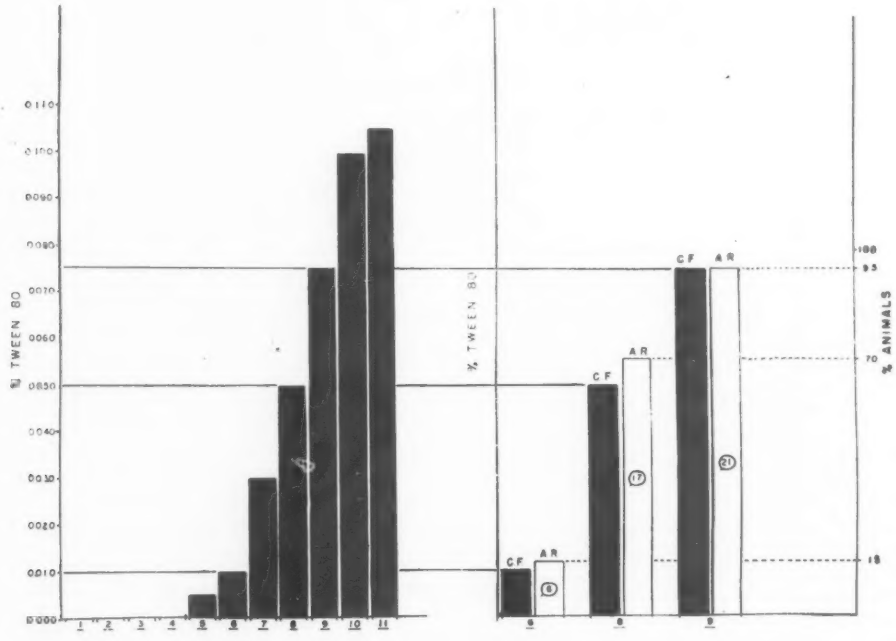

Fig. 2.—Titration of cord formation of various strains of *Mycobacteria* and their relation to duration of allergy in animals inoculated with standard doses of the three of these strains. 1=H_{37} Ra, 2=Avian (Kirschberg), 3=M. 607 (Sm. sensitive), 4=M. 607 (Sm. resistant), 5=R_1 Ra, 6=BCG (Strain 3), 7=BCG (Strain 2), 8=BCG (Strain 1), 9=R_1 R_v, 10=Bovine (Ravenel), 11=H_{37} R_V.

C. F.=Cord Formation Titer, A. R.=Allergy Retained, O=Number of guinea pigs with allergy retained.

one incorporates a weak dilution (0.005%) of neotetrazolium chloride in the media, or adds a drop or two of it (0.1%) to the surface of the growth and reincubates for half an hour. In such circumstances every growing point assumes a deep blue color. This has been done effectively by Mudd and his associates[12].

duced to blue formazan within the body of the bacillus if the latter is living and the process indicated below is carried out. Confirmation of this is required by further study which is now in progress. This study to date comprises 7 cases of resected tissue in which data on cultures are complete, and these are presented in Table

TABLE 1

In the 7 cases here reported, neotetrazolium reduction compares favorably with routine cultures when there are sufficient bacilli for reduction study. Less than five (5) bacilli found on direct smear makes an evaluation of neotetrazolium chloride reduction impossible. A comparative study of more than this number must be made to determine the presence of or lack of reduction.

Pre-operative Data		*Post Operative Examination of Tissue*				
		Gross Appearance of Lesion		*Tubercle Bacilli*		
Patient	*Duration of SM Prior to Oper. (months)*	*Air-bearing*	*Non-air-bearing*	*Direct &/or conc. smear*	*% bacilli c N.T.C. reduction*	*Routine 8 wks. cult. &/or animal*
G. W. N.	7	Cavity*		++	58	Pos.
			Cavity	+	<5	Neg.
J. R.	18	Cavity		+	20	Pos.
			Cavity	+	<1	Neg.
C. B.	3½	Cavity		+++	35	Pos.
			Tubercle	Neg.	—	Pos.
C. S.	8	Cavity		Neg.	—	Pos.
J. A.	4	Pulmonary tissue adjacent to cavity		**+	—	Neg.
			Cavity	**+	Neg.	Neg.
E. Mc.	8	Pulm. tissue		**+	—	Neg.
			Cavity	+	Neg.	Neg.
S. H.	7½	Cavity		+	Neg.	Neg.

* The term cavity is used loosely in the literature, for example, "inspissated" cavity. In this study all so-called non-air-bearing cavities were filled with caseous tissue that was dry, semi-dry or liquefied.
** <5 bacilli found on all slides: too few organisms to evaluate neotetrazolium reduction.

3. STUDY OF RESECTED PULMONARY TISSUE. The viability test with tetrazolium may have another application in respect to the very recently developed interest in the recovery of acid-fast bacilli from tuberculous lesions in pulmonary tissue removed after chemotherapy. In these circumstances acid-fast bacilli are usually readily demonstrable by stain, but they may fail to grow on culture[1-4,7,11,16]. Much speculation exists regarding the exact viability status of these bacilli, but it appears that neotetrazolium can be re-

1. This table indicates essentially that tubercle bacilli recovered from open (air-bearing) cavities and shown on stain reduce neotetrazolium within their bodies and also grow well on culture, and that those from material in closed cavities, although numerous by smear and stain, usually fail to grow on culture and fail to reduce neotetrazolium. These impressions are derived from handling resected tissue in the following manner.

Tissue in question which is usually the caseous content of a cavity or pre-

sumed (filled) cavity, is ground and thoroughly mixed with equal parts of 0.01% neotetrazolium chloride contained in Dubos' basal medium[5] with 0.02% Tween 80, 0.5% glucose, and the whole adjusted to pH 7.2. All these ingredients and relationships seem to be necessary for maximal metabolic activity. These suspensions are made in tubes of small diameter and incubated for reading at 48 to 72 hours when slides are prepared and stained by the Ziehl-Neelson method, except with 1% malachite green as counterstain. When reduction of the tetrazolium has occurred, the red bacilli present blue "dots" at areas of (presumed) greatest metabolic activity*.

The following brief notes on one case history will illustrate the essential facts in the circumstances and indicate the possible significance of the procedure.

Case Report. G. B. N., Case No. 13,991. A white male of 51 years with far advanced pulmonary tuberculosis received streptomycin, 1 gm. twice a week and PAS, 12 gm. per day, for 7 months up to resection of the left upper lobe for residual lesions. His sputum was positive for the first 4 months of drug treatment and negative thereafter.

The specimen revealed two cavities: one air-bearing and one non-air-bearing, each containing caseous material. In each, considerable and approximate numbers of acid-fast bacilli were present on direct and concentrate smear. In the caseous material from the air-bearing cavity, 58% of the bacilli reduced neotetrazolium chloride to blue formazan within the bacillary body when properly exposed. On the other hand, less than 5% of bacilli from the closed or non-air-bearing cavity reduced this salt.

Routine cultures of material from the air-bearing cavity grew out in the usual 6 to 8 weeks period. Cultures of material from the non-air-bearing cavity were negative at this time, yet the same material grew bacilli when planted on media containing 10 mcg. of streptomycin per cc. And when all culture tubes (with and without streptomycin, 10 to 400 mg. per cc.) were incubated for 16 weeks, growth occurred on all.

Do such results indicate that living bacilli (the 58% reducing neotetrazolium) in the open cavity grow abundantly and in 6 to 8 weeks yield full development on culture medium and that the very few (less than 5%) living bacilli in the non-air-bearing area required a much longer time to produce manifest growth? This matter is under active study.

Summary and Conclusions. 1. The tetrazolium salts have the capacity to indicate viability of bacterial suspensions by undergoing reduction to either red or blue formazan, as the case may be, in the presence of living cells if proper techniques are carried out.

2. These substances can be used to standardize inocula so as to insure comparable doses of bacterial suspensions to animals.

3. When incorporated in media or added to cultures and incubated briefly, neotetrazolium is reduced at points of growth and this greatly facilitates colony counting and enhances the photogenicity of cultures.

4. Neotetrazolium may be of aid in determining whether non-growing tubercle bacilli recovered from tissue after chemotherapy and excision are viable or not.

* At once someone will say "Much granules". It is true that these areas which reduce the tetrazolium to blue formazan within the bacilli are blue and resemble to some extent the blue or black Much granules. However, bacilli from the same source fail to reveal such dots when stained conventionally. Furthermore, Much's granules tend to be present at any point in the bacillary body and the blue formazan areas tend to be polar. So it seems logical and proper to associate the blue discoloration with metabolic phenomena.

ACKNOWLEDGMENTS. Drs. Marshall G. Morris and William F. Hollister, of McCain and Pinehurst respectively, are the surgeons who provided the material for that portion of this paper which deals with study of resected pulmonary tissue. Without their full cooperation in the work, this part of the paper could not have been done. This is a note of thanks to them.

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PLASMA LIPOPROTEIN CHANGES INDUCED BY ACUTE LOCAL COLD INJURY

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GOFMAN *et al.*[2] observed that atherosclerosis in rabbits and men is associated with increased levels of the cholesterol-bearing S_f 12-20 and S_f 20-100 classes of serum lipoproteins. Pollack[6] reported that vascular lesions resembling atherosclerosis were noted at autopsy in children who had died after acute traumatic episodes. In this laboratory, significantly increased concentrations of serum cholesterol were observed in rabbits rendered hypersensitive to horse serum[7], a treatment reported to be associated with acute tissue breakdown[10]. These reports suggest that acute traumatic injury is associated with both atherosclerosis and an increase in the serum levels of certain lipoproteins. It was decided, therefore, to subject rabbits to trauma in the form of acute, severe, local cold injury and measure the changes in the blood lipoproteins.

Methods. Sixty albino male rabbits of the New Zealand strain were selected from the colony in this laboratory and numbered consecutively. The animals weighed approximately 2 kg. each and were maintained in an air-conditioned room on standard commercial feed and water, *ad libitum*, prior to and throughout the experiment. Twenty cubic centimeters of blood were taken from each rabbit by cardiac puncture with a lightly heparinized syringe and the packed cell volume determined on a small portion of each sample. The remaining blood was centrifuged, the plasma* separated, and each sample labeled with the rabbit number plus the designation "pre" indicating "pre-trauma." Care was exercised during drawing and handling of the blood to avoid hemolysis. The samples were analyzed for total protein, total cholesterol, lipid phosphorus, and the concentrations of the S_f 12-20 and 20-100 classes of lipoproteins. The analytical procedures, as done in this laboratory, have been previously described[8]**. Immediately following the initial blood sampling, the right hind leg of each rabbit was shaved and depilated according to the technique of Pichotka and Lewis[5].

Twenty-four hours after depilation, the rabbits were tied to animal boards with their shaved right hind legs dangling below the level of the board. Each shaved leg was lightly greased with sulfamylon ointment and

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* It should be noted that lipoprotein analyses herein reported are given for blood plasma. Thus far, literature by the present authors and others have recorded lipoproteins in blood serum. Data taken in this laboratory demonstrate that plasma and serum give identical results. Dr. John Gofman has confirmed this finding in a personal communication.

** Determination of phospholipid has since been modified to include a change suggested by Dr. Harry Albaum of Brooklyn College. This modification consists of direct color development in the digestion tube.

fitted with a rubber sheath. Wherever the sheath fitted loosely it was secured with adhesive tape. The rabbits were then divided into two equal groups. The control rabbits were allowed to remain secured to the boards with their shaved and covered right hind limbs suspended in air at 25° C. for a period of 30 minutes. The experimental group of rabbits, secured in the same position, were subjected to a standardized local cold injury of the right hind limb by suspension in an alcohol-water bath at −12°C. for 30 minutes. The details and mechanics of the cold exposure have been described by Pichotka and Lewis[5]. All rabbits were then taken off the boards and the rubber sheaths removed from the exposed right limbs. Sulfamylon ointment was applied and the legs dressed with roller bandages. Twenty-four hours after exposure, a blood sample was taken from each rabbit, packed cell volume determined, the plasma separated, and each sample labeled with the corresponding rabbit number, plus the prefix "post" indicating "post-trauma." The "post" samples were chemically and physicochemically analyzed exactly as were the "pre" samples. The "pre" value was subtracted from the "post" value and recorded as a positive or negative net difference for each of the control and traumatized rabbits. Mean net differences were then taken for each experimental variable and the significance level of the net effect of local cold injury recorded in terms of "P." These results are shown in Table 1 and Fig. 1.

TABLE 1.—MEAN VALUES FOR VARIOUS OBSERVATIONS OF BLOOD AND PLASMA CONTENT IN CONTROL AND COLD INJURED RABBITS

	Control			*Cold Injured*				
	Pre value	*Post value*	*Change*	*Pre value*	*Post value*	*Change*	*△Change*	*P***
Cholesterol mg. per 100 cc.	49.5	54.4	5.0	52.2	119.3	67.1	64.28	<0.0001
S_f 12–20 Lipoproteins mg. per 100 cc.	27.1	40.6	13.4	33.3	102.5	69.2	55.46	<0.0001
S_f 20–100 Lipoproteins mg. per 100 cc.	24.8	56.8	31.9	35.7	>181.7*	>146.0*	>113.41*	0.002
Total protein gm.%	5.7	5.5	−.2	5.3	4.8	−.5	−0.29	0.08
Packed cell volume %	41.0	33.4	−7.6	40.3	33.8	−6.5	1.47	0.21
Lipid phosphorus mg. per 100 cc.	4.3	5.1	.8	4.0	8.2	4.2	3.35	<0.0001
Lipid phosphorus to cholesterol ratio × 10	.97	1.0	.03	.90	1.0	.1	0.07	>0.50

* Some observations were greater than the maximum value which could be measured. In these cases the maximum observable value was used.

** P = probability that △ change is due to chance.

Discussion. The data indicate that plasma lipoprotein levels are very sensitive to local cold injury. The S_f 12-20 class of lipoproteins shows an average increase of 69 mg. per 100 cc. in cold-injured rabbits, of which only 13 mg. per 100 cc. is accountable on the basis of blood sampling (compare with controls). The S_f 20-100 class of lipoproteins shows a change of even greater magnitude in the same direction (see Fig. 2). Plasma cholesterol concentrations in control rabbits showed no significant increase, whereas as corresponding levels in the experimental animals showed a mean increase after cold exposure of 129%. These data suggest a link between the observations of Pollack, who noted atherosclerosis following acute trauma; and Gofman, who reported increased blood levels of lipoprotein associated with atherosclerosis.

The increased concentration of lipoprotein in the cold-injured rabbits after trauma cannot be accounted for on the basis of hemo-concentration. The data indicate that there is no significant effect of cold exposure alone on either packed-cell volume or total plasma-protein concentration. If anything, a significant hemo-dilution was

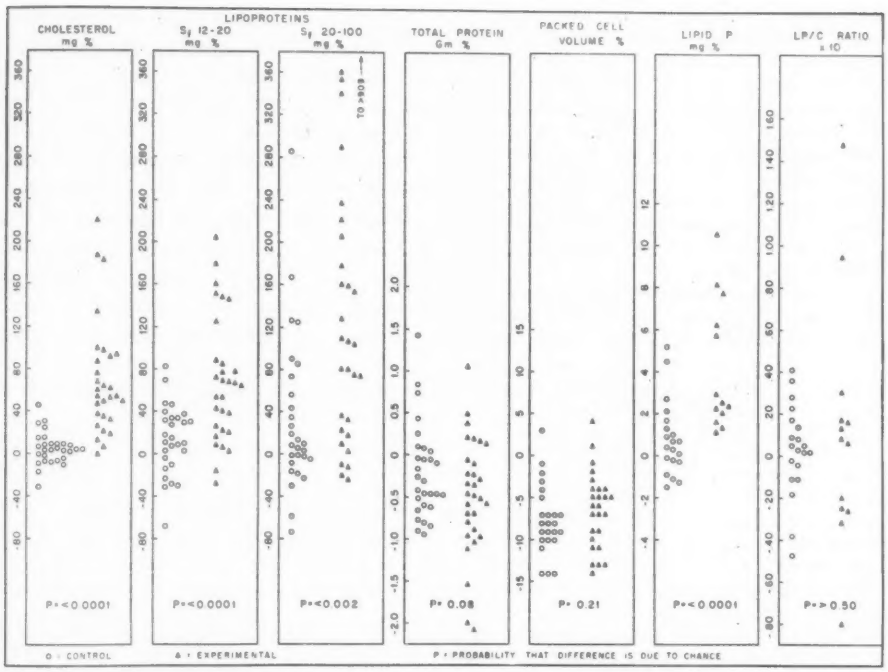

FIG. 1.—Distribution of changes in blood variables induced by local cold injury ("post" value minus "pre" value—see text).

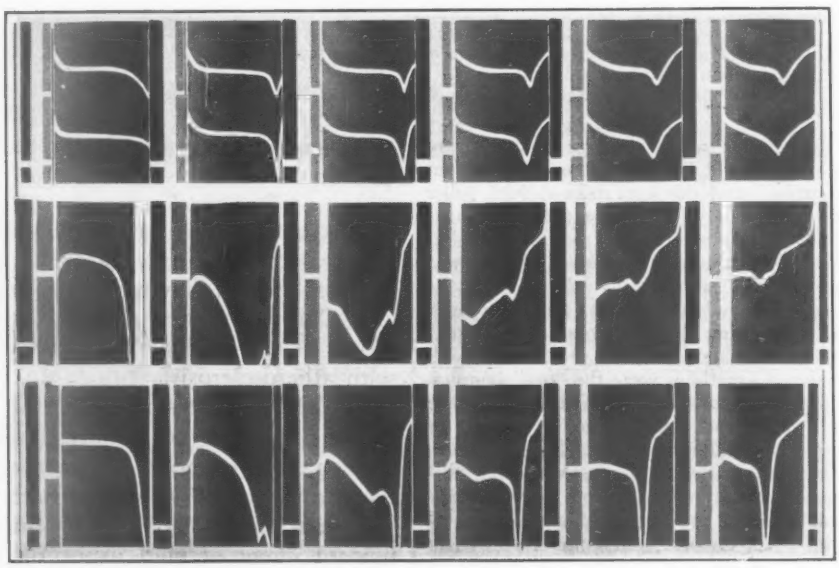

FIG. 2.—The upper figure is the ultracentrifuge pattern of the plasma top fraction prior to cold exposure in two rabbits. The lower figures are the patterns in the same animals after local cold injury.

noted in both control and traumatized groups, probably due to the pre-bleeding. Consequently, we must consider the increased cholesterol concentration observed as a result of cold injury to reflect a marked increase in total circulating cholesterol. In this regard, it is interesting to recall the findings of Schwenk and Werthessen[9] who perfused whole pig liver in organ culture. These investigators reported that when the perfused organ was excised and cultured with minimum damage and handling, there were produced only small amounts of labeled cholesterol from C^{14} tagged acetate introduced into the perfusate. If, on the other hand, the liver was rendered anoxic during the perfusion, *or physically damaged by slashing with a knife blade,* the uptake and conversion of acetate to cholesterol was increased several hundredfold. It would seem that tissue cells synthesize increased amounts of cholesterol as an integral portion of the repair process and that possibly the higher level of plasma lipoprotein observed in this present experiment originated in the regenerating tissue of the traumatized rabbit leg.

Sufficient plasma was available to allow analysis for lipid phosphorus in 33 animals. These data demonstrate a significant increase in phospholipid as a result of local cold injury. Gertler and Garn[1] have suggested that the phospholipid in blood tends to stabilize the cholesterol colloidal sol and thus inhibit the deposition of cholesterol in the arterial intima.

The relationship between plasma phospholipid and cholesterol is shown as the lipid phosphorus to cholesterol ratio in Table I. It will be noted that, in spite of the increased levels of both variables, local cold injury induced no significant change in the ratio. The increased levels of phospholipid noted in the present experiment may be a manifestation of a homeostatic effort on the part of the injured organism to minimize possible damaging effects of increased cholesterol concentration.

In a histologic study, Lewis and Moen[4] demonstrated that identical lesions can be produced in rabbit muscle by either cold, heat, or tourniquet injury. These authors point out, however, that cold is less efficient than heat but more efficient than ischemia as a means of producing the necrosis. It will be interesting to determine whether or not this quantitative variation is reflected in the plasma lipoprotein patterns of rabbits subjected to the different types of trauma.

The Gofman group has reported that the increased levels of atherogenic lipoproteins observed in cholesterol-fed rabbits can be inhibited by heparin administration[3]. If similar inhibition can be achieved in traumatized rabbits such data may tend to strengthen the etiological relationship between traumatic injury and atherosclerosis that was suggested by Pollack. These latter problems are receiving continued study in this laboratory.

Summary. Plasma lipoprotein levels were determined in rabbits subjected to acute local cold injury. Plasma cholesterol, presumably transported in the blood as a protein conjugate, was increased markedly in the traumatized animals. Highly significant increases were also noted in the plasma concentrations of the S_f 12-20 and S_f 20-100 classes of lipoproteins. That these increases were not the result of a hemoconcentration was established by the fact that little change in either packed-cell volume or total protein concentration of the blood plasma could be recorded. The data are discussed with regard to the possible source of increased lipids and, also, with respect to a possible etiologic relationship between traumatic injury and atherosclerosis.

For explanation of interpretation of ultracentrifugal plates see Redmond *et al.*[8]

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REACTIVATION OF PULMONARY TUBERCULOSIS IN RELATION TO SUBTOTAL GASTRECTOMY FOR PEPTIC ULCER*

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Gastrectomy for relief of peptic ulcer has, in the past 10 years, become one of the most frequently performed major operations. There is little discussion in American medical literature of any adverse effect of such gastrectomy upon inactive, arrested or even active pulmonary tuberculosis. The Continental journals, on the other hand, have carried a number[1,4,6] of papers on this subject. These investigators are in general agreement that gastrectomy exerts a distinctly adverse effect upon inactive or arrested tuberculosis. From 1 to 15 months after the operation, an acute, exudative tuberculous pneumonia may develop, which terminates fatally in a few months in approximately 25% of those infected. Almost all of the patients were believed to have been in good health before their surgical episode, but few had received the benefit of a chest roentgenogram at that time. One Gallic phthisiologist[1] reported that 3% of the 742 patients in his sanatorium carried gastrectomy scars on their upper abdomens. It was suggested by these investigators that gastrectomy for peptic ulcer should be reserved for those patients with obstruction or exsanguinating hemorrhage, when these individuals in addition carry a definite lesion of tuberculosis in their chest film. A variety of neural, vegetative, humoral, hormonal, metabolic and nutritional hypotheses were submitted by them in explanation of this observation.

Our attention and interest in this direction was aroused by encountering 7 instances of the combination in the past 4 years (Table I). Seven of the 142 patients with pulmonary tuberculosis admitted to the West Roxbury Veterans Hospital during this period and subsequently transferred to a tuberculosis hospital had formerly been subjected in this hospital to gastrectomy for peptic ulcer. In addition, the well recognized association of tuberculosis with alcoholism or Laennec's cirrhosis was apparent. There were also 7 patients

TABLE 1.—CONCURRENT DIAGNOSES IN 142 PATIENTS FOUND TO HAVE TUBERCULOSIS IN THIS HOSPITAL BETWEEN JULY, 1946 AND JUNE, 1950.

Concurrent Diagnoses:	*No. of Patients*
Alcoholism	18
Diabetes mellitus	7
Post-gastrectomy	7
Laennec's cirrhosis	6
Marie-Strümpel arthritis	3
Other operations	2

* Presented at the 65th Annual Meeting of the American Clinical and Climatological Association, October 16-18, 1952, at Elmira, New York.

with both diabetes and tuberculosis. During that same period 356 gastrectomies had been performed for various ulcer disorders, an incidence of 2% of all of our gastrectomized patients who developed subsequent serious tuberculosis. Our overall admission rate for tuberculosis was 0.5%. This is slightly less than the 0.8% figure reported for the Veterans Administration case-finding survey program[5] in the screening of inpatients.

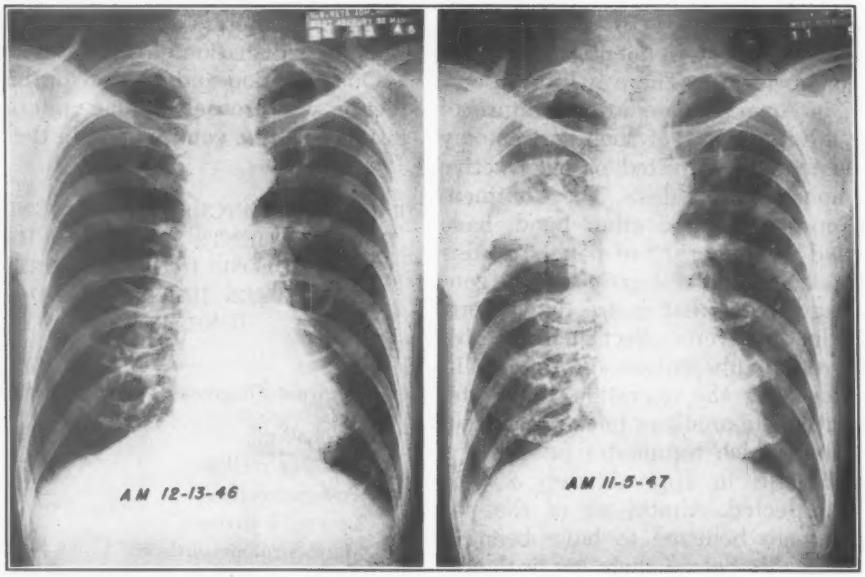

FIG. 1.—Chest films of patient A.M. (Case 1) before gastrectomy and 10 months after operation.

Of our 7 patients, 2 have died; 2 are in a sanatorium with chronic, far advanced active disease, with a "fair" prognosis; 2 are arrested, having had extensive thoracic surgery; and one is cured. This record is striking in its poorness.

Case Reports. CASE 1. A.M., a 50-year-old electrician, was first seen in December, 1946, following a moderate hematemesis. A gastric ulcer was demonstrated by Roentgen-ray, which did not decrease in size during 3 weeks of medical therapy. His chest film (Fig. 1) was interpreted as showing only a large Ghon tubercle in the periphery of the right upper lung field, but re-evaluation later, demonstrated a small soft lesion above this behind a rib. Upon failure to heal the ulcer, an elective gastrectomy was performed. He was seen repeatedly in surgical follow-up clinic because of vomiting and weight loss. The latter totalled 20 pounds within 10 months of the operation and he was readmitted in November, 1947, for investigation. A chest film (Fig. 1) revealing extensive pneumonic involvement on the right, and a positive sputum examination promptly explained some of his difficulties. He was transferred to a tuberculosis hospital. There he did poorly, with spread to much of his left lung in spite of streptomycin therapy. He signed out against advice in April, 1949, while in a terminal state, and died shortly thereafter.

CASE 2. D.F., a 59-year-old laborer, was admitted in November, 1947, because of vomiting, epigastric pain and tarry stools. He weighed 120 pounds and was moderately anemic. Gastrointestinal Roentgen studies revealed a large, ragged ulcer, high on the lesser curvature, which suggested a gastric malignancy. His chest film (Fig. 2) was interpreted as normal, but in retrospect did have

a few small hard areas suspicious of old tuberculosis in the right upper lobe. A high, subtotal gastrectomy was performed and a benign ulcer removed. He was followed in the clinic for one year and did well, gaining 15 pounds in weight. In his 13th postoperative month vomiting appeared, with inability to retain any food except liquids. Weight loss of 15 pounds developed rapidly; cough and fever were noted in February, 1949, and he was readmitted in March. Chest film (Fig. 2) revealed extensive, bilateral, acute, tuberculous infection with cavitation. The sputum was strongly positive for tubercle bacilli and a marked hyperglobulinemia was present. His temperature and pulse were high and he expired on the 10th hospital day. Necropsy permission was not obtainable.

tive for tubercle bacilli. On a regimen of bed rest, the lesion shrank and became less fluffy (Fig. 4), but his epigastric distress and gastric ulcer increased in severity and size. The pulmonary lesion was considered to be improving, and 1 gm. of streptomycin was injected daily for 28 days, and a subtotal gastrectomy for a benign gastric ulcer was undertaken at the end of the first week of this therapy in mid-November, 1948. He returned to the same rest regimen that he had been on before operation; but could not eat well, and lost 5 pounds. A chest film 2 months later in mid-January, 1949, showed that a considerable spread had occurred, cavitation quickly developed and he was transferred to a tuberculosis hospital. There he had several surgical procedures including a Schede's thoracoplasty

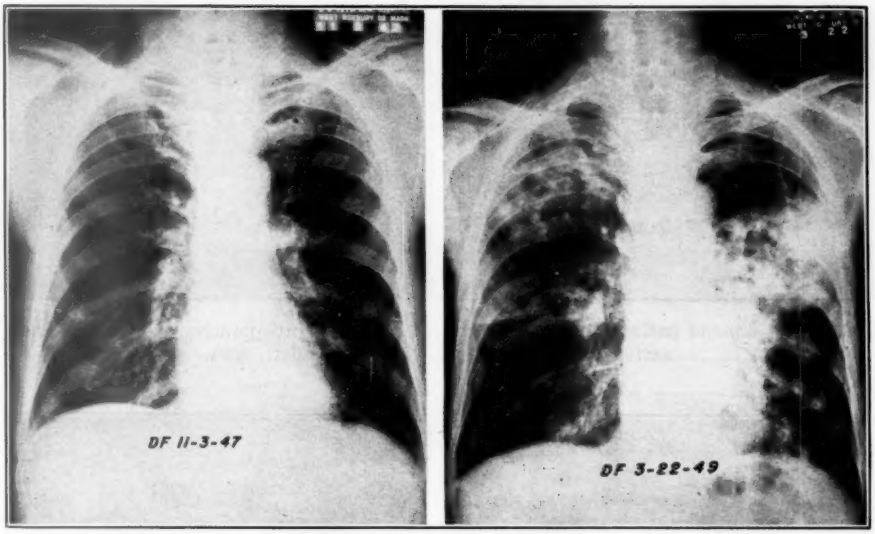

FIG. 2.—Chest films of patient D.F. (Case 2) prior to gastrectomy in December, 1947, and just before his death in March, 1949.

CASE 3. J.P., a 42-year-old golf course caretaker, was first seen in March, 1948, because of nervousness, alcoholism and epigastric distress. A gastrointestinal series revealed a moderate sized ulcer on the mid-lesser curvature wall of the stomach. His chest film was believed normal (Fig. 3). He was followed closely, stopped drinking and gained weight. He was then readmitted for treatment of varicose veins. The chest film (Fig. 3) in September, 1948, after an interval of 5 months now demonstrated a soft, fluffy exudative lesion in the infra- and supraclavicular regions. Three gastric washings were negative in March, 1950. He was discharged in September, 1950, and has done well in the past 2 years.

Discussion.—Our 7 patients had an average age of 46 years, the youngest being 34 and the eldest 59 years. It is interesting that 4 had suffered from gastric ulcers and only 3 from duodenal, although 4 times as many of the latter had been subjected to gastrectomy in our hospital. All had lost weight in the

months prior to the onset of symptoms referable to their pulmonary disease. This loss averaged 11 pounds for the group. In 5 instances it began immediately after the operation, but was delayed in two. The "dumping syndrome" was not prominent. Jones[2] has shown that approximately 15% of patients subjected to subtotal gastrectomy will develop a nutritional problem of real importance, with an average weight loss of 16 pounds. It seems likely, therefore, that this disturbance was of significance in our patients.

Active tuberculosis prior to operation was noted only once (Case 3) on

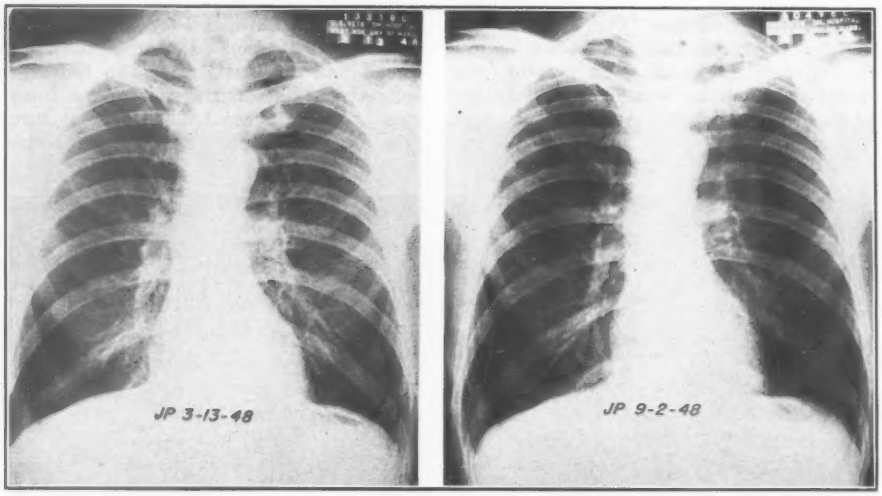

FIG. 3.—Chest films of patient J.P. (Case 3) during period of preoperative observation, showing active tuberculosis appearing at the left apex.

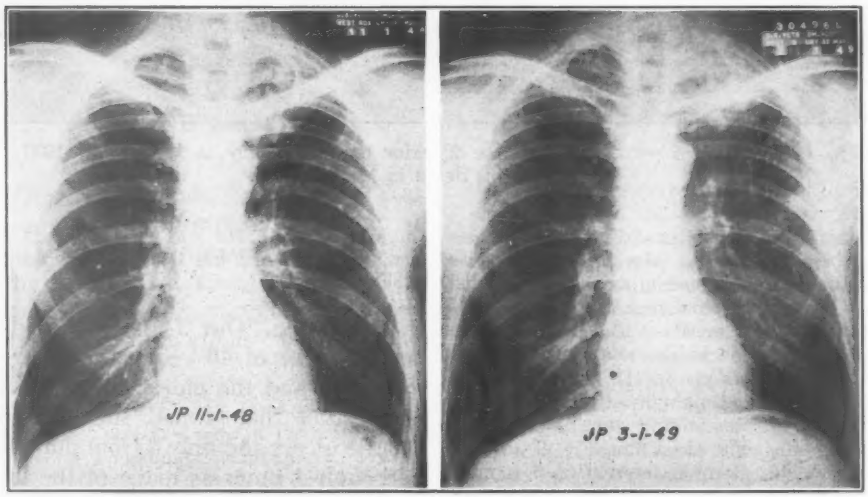

FIG. 4.—Chest films of patient J.P. (Case 3) taken just before gastrectomy, demonstrating improvement, and the exacerbation with cavitation that appeared 2 months after operation.

routine Roentgen-ray interpretation. Healed residuals of tuberculosis were originally diagnosed 5 times, but careful re-examination demonstrated small soft lesions in 2 of these patients' films. One patient had a completely normal chest film at the time of operation, and incidentally had the longest interval (2 years) before the onset of his active tuberculosis, a combination that is very likely entirely fortuitous. The 2 patients with small soft lesions prior to operation were found to have active tuberculosis within 3 months of their operation, and the remaining 4 with inactive-appearing infections became ill from 6 to 14 months later. These meager data suggest that it was not the anastomosis of the gastric stump to the jejunum that was important, but some other incident secondary to the surgical procedure, and that the more active the pulmonary infection at the time of operation, the earlier pulmonary symptoms were likely to appear. The mortality rate of over 25% and the severe acute pneumonic nature of the tuberculosis infection, are worthy of emphasis.

No detailed investigation of the possible factor or factors of immunity operating to provoke a reactivation of pulmonary tuberculosis was undertaken. It is unlikely that the anesthesia played any role, as the patient's disease was usually activated some months after operation, and current thoracic surgical operations for tuberculosis itself have indicated the safety of modern anesthesia in this respect. Several thousand other abdominal operations were performed at this hospital during this period, but tuberculosis followed only twice.

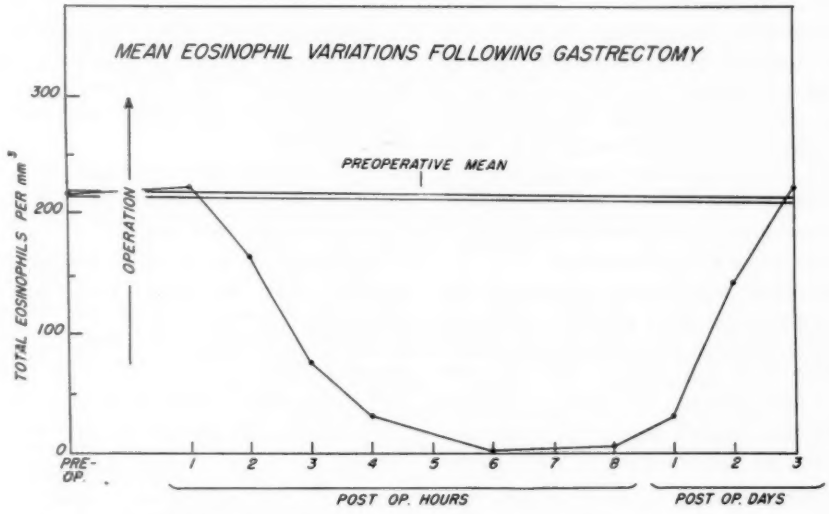

FIG. 5.—Mean total eosinophil count variations of 9 patients after gastrectomy.

ACTH and cortisone have been officially recognized by the American Trudeau Society as exerting an adverse effect on the course of active tuberculosis. The total eosinophil counts of 9 patients before and for several days after gastrectomy were studied to decide whether any unusual stress phenomena were in evidence after this particular operation. In spite of the fact that most of the patients were losing weight during this time, the eosinophil counts had returned to the pre-opera-

tive level by the third postoperative day (Fig. 5) and remained there. No such studies were made in the 7 patients who developed tuberculosis. No urinary corticoid studies were made, so we cannot assess the factor of stress and cortisone.

There seems to be an effect on resistance to tuberculosis that is known to be associated with weight loss and malnutrition. Good experimental evidence of the effect of a low-protein diet on lowering resistance to tuberculosis in rats, has been demonstrated by Long[3]. Clinically the extremely high incidence of tuberculosis among prisoners of war, or internees in concentration camps, is above that expected from contact alone, and supports the ancient observation that loss of weight as well as stress somehow predisposes an individual towards tuberculosis.

The acute, exudative nature of the tuberculous process should make it amenable to therapy with streptomycin and PAS. It is quite likely that we permitted our patients to attain a degree of infection, which made them less responsive to chemotherapy. It seems reasonable to believe, however, that if the physician is aware of this hazard and carefully follows with serial chest films the gastrectomized patient who is losing weight, he should detect such reactivations early and avoid the mortality and morbidity experienced by our patients.

Summary.—1. Two per cent of 356 patients with peptic ulcer treated by gastrectomy subsequently developed active pulmonary tuberculosis. Healed tuberculosis was usually present before operation, and weight loss preceded the onset of pulmonary symptoms, some months later. The mechanism in the breakdown of immunity was not further defined.

2. The pulmonary infection was notable for its acute pneumonic nature and high mortality rate (25%).

3. Recognition of this hazard with careful and repeated post-operative chest roentgenograms of the gastrectomized individual in negative nutritional balance, with healed or apparently inactive tuberculosis, should reduce the seriousness of this complication.

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PROGRESS
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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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STUDIES OF SYPHILIS OF THE EAR AND PENICILLIN

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THE correlation of the histopathologic, serologic, bacteriologic and clinical findings[1a,b,d,e,f,2,3,5a,b,9,10,12,24,31a.b,32a,b,35,52,53,57a,b,69] has established syphilis of the inner ear as a definite entity. On the basis of histopathologic studies of the internal ear, some writers [15,23,27,28,38,47,48,66] were of the opinion that congenital and acquired syphilis each produced specific lesions, while others[1a,b,d,e,f,29] disagreed with this observation. An accordance seemed to exist on the point that there was a relation of the incidence of hearing impairment to the type of syphilis of the person [1f,18,40a]. In spite of this fact, some authors[13b,17a,c,18,19] have stressed in their reports that the incidence of hearing impairment was similar in syphilitic and non-syphilitic patients of the same age, sex and race. This divergency is chiefly the result of the controversy still prevailing in the diagnostic problem of syphilis of the internal ear on a clinical basis, which of necessity is generally an inferential one.

The clinical diagnosis of syphilis of the 8th cranial nerve has been based on the following criteria[1f] (1) loss of acuity for high tones and a lowered upper tone limit, (2) loss of acuity for high tones accompanied by a loss of middle tones or for all tones by air conduction and impaired bone conduction, (3) impairment of vestibular reaction, (4) shortened bone conduction with normal air conduction, (5) vestibular paradox[1f], (6) Hennebert's fistula sign[33], and (7) positive complement fixation tests on blood and spinal fluid. The first three premises merely signify nerve involvement without designating the etiological agent. The soundness and incidence of the fourth premise remain a disputed question respecting the sign being pathognomonic of syphilis of the 8th nerve. The frequence of the occurrence of the fifth and sixth premises is not high enough to be of diagnostic significance. The last premise does not *per se* localize the syphilitic lesion to the inner

ear. On the basis of the foregoing, it is apparent that there is considerable dispute regarding the incidence of syphilitic infection of the 8th cranial nerve[1f,18,19,13b,40a,53,73].

A survey of the current literature indicates that notable progress has been achieved in syphilotherapy since penicillin has practically supplanted chemotherapy[20,46]. In contrast, a review of the recent literature impresses one with the paucity of material on syphilis of the ear. Cognizant of this fact, we felt that the time was ripe for a re-evaluation of the subject. The chief purpose was to determine in a clinical and statistical manner the validity of the prevailing well-entrenched concepts since the introduction of penicillin therapy, and to evaluate the efficacy of penicillin-therapy respecting its prophylactic and therapeutic usefulness in aural syphilis.

SELECTION OF PATIENTS. Fully aware of the foregoing views, our principal concern was to collect a sufficiently large group of patients who, in spite of a severe and strict screening, would meet specified criteria of diagnostic definition. With this aim in mind, we undertook a comprehensive study of 310 consecutive patients (Table 1) with an established diagnosis of syphilis, comprised of random samplings of each type of syphilis of both sexes in each age group. The type of syphilis was diagnosed by syphilologists. Those with hearing loss prior to acquisition of syphilis were excluded from the study. The higher incidence of males and colored patients was due to chance.

PROCEDURE. Four patients with early congenital syphilis were considered separately, reducing the series to 306 patients. The hearing acuity of the latter was evaluated by voice tests, Edelmann weighted steel forks and ADC audiometer 50E2. Forks C to c^5 were used to determine the high and low limits. Masking was applied for the audiogram, bone conduction, and when indicated, for air conduction. The vestibular mechanism was evaluated by rotation and minimal stimulation, when indicated by maximum caloric and galvanic stimulation, and by spontaneous symptoms and signs. Each patient received a complete otorhinolaryngological examination.

Of this group, 17 patients with conductive hearing loss were eliminated from the hearing tabulations. The application of this rule, reduced the total to 289 patients for hearing analysis. In Table 2, a composite of the different hearing groups as found in the different types of syphilis is shown allocated in accordance with age, sex and color of the patient. The poorer ear was used for classification whenever a marked difference in hearing existed for two ears.

In each type of syphilis, the hearing acuity of the patient was classified in conformity with the pattern of the audiogram into 3 main groups[4,13a,b,17a] (Table 3): normal, excessive high tone loss, and subnormal. The normal hearing group was divided into subgroups A and B on the basis of the following criteria: Sub-group A consisted of patients with audiogram, range to voice and fork tests, and bone conduction normal; Sub-group B included patients essentially identical except for impaired bone-conduction (g^1, c^2, and g^2 forks). The group of excessive high tone loss was also broken up into subgroups A and B on the basis of the following requirements: Sub-group A comprised of patients with range to voice and bone conduction normal but the high limits by fork (c^5) and audiometer were lowered; Sub-group B consisted of patients essentially alike except for shortened bone conduction. The subnormal group embraced the

TABLE 1.—DISTRIBUTION OF PATIENTS ACCORDING TO AGE, SEX, COLOR, AND TYPE OF SYPHILIS

	Type of Syphilis																				
	Early Congenital				*Late Congenital*				*Early Syphilis*				*Early Latent*				*Late Latent*				*Neurosyphilis*				
	White		*Colored*		*White*		*Colored*		*White*		*Colored*		*White*		*Colored*		*White*		*Colored*		*White*		*Colored*		
Age Group	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*Total*
0–10	1	0	0	3	0	1	2	11	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	19
11–20	0	0	0	0	2	7	11	17	0	0	0	1	0	0	2	5	0	0	0	0	0	0	0	0	45
21–30	0	0	0	0	2	1	2	1	0	0	2	1	4	0	13	11	3	0	8	5	1	2	4	6	66
31–40	0	0	0	0	1	0	1	0	0	1	1	0	1	0	3	0	1	2	12	5	4	3	10	3	48
41–50	0	0	0	0	0	1	0	0	0	0	0	0	1	1	1	0	4	0	9	6	16	4	19	6	68
51–60	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	1	10	4	18	1	5	3	46
61–69	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	1	0	6	2	4	0	18
TOTAL	1	0	0	3	5	10	16	29	0	1	3	2	6	1	20	16	17	3	40	20	45	12	42	18	310
White	1				15				1				7				20				57				101
Colored	3				45				5				36				60				60				209
Males	1				21				3				26				57				87				195
Females	3				39				3				17				23				30				115

TABLE 2.—DISTRIBUTION OF HEARING GROUPS ACCORDING TO AGE, SEX, COLOR, AND TYPE OF SYPHILIS

Age Group	Sex	Late Congenital						Early Latent						Late Latent						Neurosyphilis						Total
		White			Colored			White			Colored			White			Colored			White			Colored			
		N	EHT	S	N	EHT	S	N	EHT	S	N	EHT	S	N	EHT	S	N	EHT	S	N	EHT	S	N	EHT	S	
0–10	M	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
	F	1	0	0	9	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11
11–20	M	0	1	1	9	0	2	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15
	F	6	1	0	16	0	1	0	0	0	5	0	1	0	0	0	0	0	0	0	0	0	0	0	0	30
21–30	M	2	0	0	2	0	0	2	2	0	13	2	0	2	1	0	7	1	0	1	0	0	3	0	1	39
	F	0	0	1	1	0	0	0	0	0	10	0	1	0	0	0	3	1	0	0	1	1	6	0	0	25
31–40	M	0	1	0	0	0	1	1	0	0	3	1	0	1	0	0	11	1	0	1	0	3	7	2	1	34
	F	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	4	0	1	0	2	1	2	1	0	13
41–50	M	0	0	0	0	0	0	1	0	0	1	0	0	2	2	0	6	2	1	5	6	5	8	4	5	48
	F	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	4	0	0	2	1	1	2	2	1	15
51–60	M	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	6	1	3	0	6	11	2	1	2	35
	F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	2	0	0	6
61–69	M	0	0	0	0	0	0	0	0	0	0	0	0	2	0	3	1	0	0	3	0	3	1	0	2	15
	F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
TOTAL		9	3	3	39	0	5	5	3	0	34	3	2	9	5	3	46	6	5	12	16	26	33	10	12	289

Legend: N—Normal Hearing Group
S—Subnormal Hearing Group
EHT—Excessive High Tone Loss Group
M—Male
F—Female

patients with a narrowed range to voice, forks, and audiometric tests associated with an impaired bone conduction.

SYMPTOMATOLOGY. *Impairment of Hearing.* Numerous reports[1f,6,16,27,32a,b,39,52,53] have appeared in the literature describing its modes of onset and sequences. In our study, 26 patients complained of bilateral loss of hearing which ranged from marked to profound. In 4, the loss proved to be conductive in nature, and the total was reduced to 22 patients distributed as follows: sudden onset occurred in 2 ent, only 3 with acute syphilitic meningitis were inconvenienced by this symptom. All had a subjective and/or objective hearing loss except for two. Vestibular symptoms are not common, because the involvement is sufficiently dilatory for compensation to develop.

Discharge. Purulent discharge was noted in 5 patients with a concomitant otitis media.

Pain. Only 1 patient had a mild otalgia. Moos and Steinbrugge[52] were of the opinion that there was some sensation of pain due to periostal growth in the labyrinth.

TABLE 3.—DISTRIBUTION OF THE HEARING GROUPS ACCORDING TO THE TYPE OF SYPHILIS

	Normal Hearing Group		*Excessive High Tone Loss Group*			
Type of Syphilis	*Subgroup A*	*Subgroup B*	*Subgroup A*	*Subgroup B*	*Subnormal Hearing Group*	*Total*
Late Congenital	45	3	0	3	8	59
Early Latent	37	2	3	3	2	47
Late Latent	49	6	3	8	8	74
Neurosyphilis	38	7	8	18*	38	109
TOTAL	169	18	14	32	56	289

* 5 cases diminished to voice tests.

late congenital syphilitics and 4 neurosyphilitics (3 acute syphilitic meningitis and 1 tabetic); and gradual onset in 3 late congenital syphilitics, 3 late latent syphilitics and 10 neurosyphilitics. In 17 patients, the hearing loss preceded treatment; in 3, it occurred years after inadequate treatment; and in 2 the onset was gradual after the completion of adequate treatment.

Tinnitus. We noted 39 patients with tinnitus, which measured from mild to disconcerting, and was bilateral except in 2. One with conductive impairment and 3 cardiac patients were eliminated. Of the 35 remaining patients, all presented some degree of hearing loss.

Vertigo. Of the 21 patients complaining of dizziness in the past or at pres-

In spite of the care we exercised in taking the histories, we were impressed with the paucity and mildness of the volunteered information. With the aid of non-suggestive questions, additional information was obtained.

Clinical Analysis of Case Material.

A. ANALYSIS OF HEARING IMPAIRMENT.

1. *General Incidence in Syphilis.* In spite of the fact that syphilitic infection of the 8th cranial nerve is a well-known manifestation, Ciocco[17a,c] Bunch [13b] and Crowe, Guild and Polvogt[19] reported that the acuity of hearing impairment is essentially similar in syphilitics and non-syphilitics of the same sex and age. In fact, they did not find syphilis responsible for auditory nerve involvement more often than any other general systemic disease. Of 286 syphi-

litic patients evaluated by Ciocco and Weinstein[18], 136, or 47%, presented nerve impairment. On this basis, they stated, "It is highly improbable that this represents an effect of age on hearing entirely independent of syphilis." In our series, 102 patients out of 289, or 35%, revealed nerve involvement (Table 2). We are of the opinion that the general incidence of hearing impairment in syphilitic persons is higher than in those without the disease.

2. *Incidence in Different Types of Syphilis.* The distribution was as follows (Table 3): 18% in late congenital syphilis; 17% in early latent syphilis, 25% in late latent syphilis; and 59% in neurosyphilis. In the latter form, symptomatic neurosyphilis accounted for 78% of the hearing defect (Table 4). The incidence in asymptomatic neurosyphilis was 29%, in acute syphilitic meningitis 100%, in tabes 84%, in taboparesis 80%, and in paresis 78% (Table 4). According to Ciocco and Weinstein[18], the distribution was as follows: 62% in congenital syphilis; 31% in early syphilis; 33% in late syphilis; and 64% in neurosyphilis. The discrepancy is most probably due to the fact that their material was not random samplings.

Our findings conform to those of previous investigators[1f,40a] in that the incidence of impaired hearing is highest in neurosyphilis, especially the symptomatic form, distantly followed by late latent, late congenital and early latent syphilis. Furthermore, it is of interest to note that the subnormal hearing group exceeded the excessive high tone loss group in late congenital syphilis, while the reverse held in early latent syphilis. In the late latent type, the subnormal hearing group commenced to gain in frequency and ultimately surpassed the excessive high tone loss group in neurosyphilis (Table 3).

3. *Incidence in Age Groups.* As anticipated[4,8,13a,b,17a,30,61,63,71,74] the hearing impairment increased with each succeeding decade except for the last one which probably occurred by chance (Table 5). Of the impaired hearing group, 66% were above the age of 51 years in spite of the fact that 80% of our series were above the same age. In the series of Ciocco and Weinstein[18], 73% of the impaired hearing group were above the age of 50 years although 77% of the patients examined were above this age. Ciocco[17a,c] and Bunch[13a,b] were of the opinion that the age period was the main factor responsible for the hearing defect entirely independent of syphilis.

Wary of the fact that the auditory

TABLE 4.—ANALYSIS OF NEUROSYPHILITICS ACCORDING TO HEARING GROUPS

Type of Neurosyphilis	*Normal Hearing Group*		*Excessive High Tone Loss Group*		*Subnormal Hearing Group*	*Total*
	Subgroup A	*Subgroup B*	*Subgroup A*	*Subgroup B*		
Asymptomatic	30	4	5	2	7	48
Tabes Dorsalis	5	1	3	8	21	38
Paresis	2	1	0	6	5	14
Taboparesis	1	0	0	2	2	5
Acute Syphilitic Meningitis	0	0	0	0	3	3
Primary Optic Atrophy	0	1	0	0	0	1
TOTAL	38	7	8	18	38	109

nerve is vulnerable to many agents, we made an effort to eliminate any other conceivable cause of nerve impairment. The incidence appears to us too high to represent the usual table of expectancy. Furthermore, the vestibules in many patients were concomitantly involved. In our opinion, the findings indicate that something more than casual factors had influenced the end results.

above 2048 d.v. Here we found the incidence in the white female practically double that of the colored male. The contention that persons of the colored race become infected at an earlier age and will, therefore, develop hearing impairment at a younger age than a white individual, was not borne out by our data. According to Stokes[62], the incidence of hearing impairment in congenital

TABLE 5.—HEARING GROUPS DISTRIBUTED ACCORDING TO AGE GROUP

	Normal Hearing Group		*Excessive High Tone Loss Group*			
Age Group	*Subgroup A*	*Subgroup B*	*Subgroup A*	*Subgroup B*	*Subnormal Hearing Group*	*Total*
0–10	12	0	0	0	1	13
11–20	37	1	0	2	5	45
21–30	46	6	4	4	4	64
31–40	30	1	1	8	7	47
41–50	27	5	7	10	14	63
51–60	11	4	2	8	16	41
61–69	6	1	0	0	9	16
TOTAL	169	18	14	32	56	289

TABLE 6.—RELATIONSHIP OF HEARING IMPAIRMENT TO SEX, COLOR, AND TYPE OF SYPHILIS

	White		*Colored*		
Type of Syphilis	*Male*	*Female*	*Male*	*Female*	*Total*
Late Congenital	3	3	3	2	11
Early Congenital	2	1	3	2	8
Late Latent	8	0	9	2	19
Neurosyphilis	34	8	18	4	64
TOTAL	47	12	33	10	102

4. *Incidence in Relation to Sex and Color of Patient.* Hearing impairment occurred in 80 (42%) males, in 22 (22%) females, in 59 (62%) white patients, in 43 (22%) colored patients, in 47 (66%) white males, in 12 (52%) white females, in 33 (28%) colored males, and in 10 (13%) colored females (Table 6).

Investigations[14,17a] have shown that with advancing age the male had a greater loss of acuity for frequencies

syphilis was higher in the male. In our series of congenital syphilis, both sexes were about equal.

Our findings can best be explained on the basis of Moore's[51b] observations: "Among white males the incidence of clinical neurosyphilis alone is greater than the incidence of both asymptomatic and clinical neurosyphilis in white females. Negro males fare appreciably better than white females, while among the Negro females clinical

neurosyphilis is relatively uncommon, and the total incidence of neurosyphilis is much smaller than in any other three groups".

5. *Incidence of Dips at 4096 d.v.* Drury[26] reported that syphilitic patients with an involvement of the auditory nerve tended to show a 'dipper curve gap' at 4096 d.v. Whenever the dip was greater than 30 db., he suspected syphilis as the cause. Ciocco[17a,c] found an equal frequency of this dip in non-syphilitics and regarded it as the initial indication of nerve degeneration which eventually included all the high tones. We encountered the following dips: 4096 in 10 patients, 2896 in 4 patients, 5792 in 3, and 8192 in 1. In 6 patients, hypoactive vestibules and impaired bone conduction were concomitant with 4096 dip, and in one each with 2896 and 5792 dips. The 8192 dip was associated with impaired bone conduction. Consequently, we can infer that dips occur in syphilitic infection of the auditory nerve but cannot imply that this relationship is limited to a single definite and characteristic dip.

6. *Rinne Test.* The Rinne test of 306 patients was evaluated with g^1 and c^2 tuning forks by determining the ratio of the duration of air and bone conduction. (Table 7). This ratio was expressed in descriptive terms suggested by Lederer[41]. The 3 patients in the subnormal hearing group with negative Rinne were included in our hearing tables because each had shortening of bone conduction and hypoactive vestibules. The response was the result of a combined effect of a middle and inner ear involvement. Mayer and Fraser[48] stated that a negative Rinne can result from ankylosis of the ossicles to each other or to the adjacent bone. (No stapedial fixation was found).

TABLE 7.—COMPOSITE OF RINNE TEST

	Rinne +					*Rinne −*			
	Normal Hearing Group		*Excessive High Tone Loss Group*						
Type of Syphilis	*Subgroup A*	*Subgroup B*	*Subgroup A*	*Subgroup B*	*Subnormal Hearing Group*	*Conductive Hearing Loss*	*Subnormal Hearing Group*	*Rinne ∝ − Subnormal Hearing Group*	*Total*
Late Congenital	45	3	0	3	4	1	0	4	60
Early Latent	37	2	3	3	1	2	1	0	49
Late Latent	49	6	3	8	7	6	0	1	80
Neurosyphilis	38	9	8	18	28	8	2	4	115
TOTAL	169	20	14	32	40	17	3	9	304
Type of response	strong positive	positive	positive	moderate shortened positive	much shortened positive				

7. *Bone Conduction.* The Schwabach test was determined by repeated trials with the audiometer and g^1, c^2 and g^2 tuning forks with masking. All patients were tested by one of us (P.I.) whose bone conduction is normal and some were evaluated by both of us. Whenever a discrepancy occurred between the audiometric and tuning forks determinations, we elected to accept the result of the latter. In patients over 50 years of age, we were most liberal in our allowance for the expected natural loss.

The distribution of the results of this procedure is given according to the type of syphilis in Tables 3 and 4; to the hearing groups and to the age groups in Table 5. Seventeen patients with conductive hearing loss had increased bone conduction. Of the 289 non-conductive cases, the bone conduction was normal in 183, and impaired in 106. As one would expect, the shortened bone conduction assumed an identical pattern as the hearing defect in its relationship to type of syphilis and age group.

8. *Disproportionate Shortening of Bone Conduction.* The phenomenon of shortened bone conduction concomitant with normal hearing by air conduction was first reported by Wanner[67] and later by others[1c,5b,11,34,40b,56,68,70]. It was observed in several diseases and head injuries. As the result of Beck's[5b] influence it was accepted by the majority as pathognomonic of syphilis. Reported incidence varied from 2 to 95%. Ciocco[17b] was of the opinion that this phenomenon occurred as often in non-syphilitics of the same age period. In our series, we encountered 18 patients with shortened bone conduction concomitant with normal hearing by air conduction. Its distribution as to type of syphilis is given in Tables 3 and 4; and as to age groups and hearing groups in Table 5. It appeared in all forms of syphilis and in each decade except the first one. According to our data, the incidence was 5.9%. Furthermore, in 13 (72%) instances it occurred in patients above 50 years of age. This incident, in our opinion, is less apt to occur in non-syphilitics of the same period. We concur with Drury[25] that shortening of bone conduction commenced at an earlier age in persons with a syphilitic involvement of the auditory nerve than in those who do not show evidence of this disease.

B. ANALYSIS OF VESTIBULAR IMPAIRMENT. Observance of the same technique was maintained by one of us (P.I.) and when necessary, repeated trials were evaluated by both of us. Unless a labyrinth convinced us of a marked degree of excitability loss, it was included in the normal category.

1. *General Incidence in Syphilis.* The vestibular mechanism of 306 patients was evaluated, and of these, 47, or 15% presented impaired vestibules (Table 8). Except for 2 patients, the involvement was bilateral. According to Ciocco and Weinstein[18], of 119 syphilitics tested, 31, or 26% had abnormal vestibules. The higher incidence found by them was probably due to the fact that their material was not random samplings. In fact, their results are even more impressive that vestibular impairment occurs more frequently in syphilitic persons than in those free of the infection.

2. *Incidence in Different Types of Syphilis.* The distribution was as follows: 9% in late congenital syphilis, 5% in early latent syphilis, 17% in late latent syphilis, and 26% in neurosyphilis (Table 8). In the latter form, symptomatic neurosyphilis was responsible for 85% of the impaired vestibules. The incidence in asymptomatic neurosyphilis was 8%; in acute syphilitic meningitis 100%, in tabes 37%, in taboparesis 40%, and in paresis 36% (Table 9). Thus, the patterns of the incidence of impaired hearing and vestibular dysfunction in their relationship to the different forms of syphilis are very similar.

An analysis of the abnormal vestibular responses in the various types of syphilis is given in Table 11. The nonfunctioning vestibules in 3 late congenitals responded to galvanic stimulation while in the neurosyphilitic no response was elicited.

3. *Incidence in Age Groups.* As observed with the hearing impairment, the incidence occurred in all decades and showed an increase in each succeeding decade, except for the last one which probably occurred by chance. In our series, 80% of the patients were above the age of 51 years. Among the group with impaired vestibules, 27 patients, or 57%, were above the same age (Table 10).

and in 2 (1%) patients, out of 187, with normal hearing (Tables 8 and 9).

7. *Relationship to Bone Conduction.* An abnormal vestibule was found in one patient with normal hearing associated with disproportionate shortening of bone conduction. In 2 patients with normal bone conduction, the vestibules were impaired. The audiogram was normal in one of the latter patients (Table 8).

TABLE 8.—ABNORMAL VESTIBULAR RESPONSES DISTRIBUTED ACCORDING TO TYPE OF SYPHILIS

	Normal Hearing Group		*Excessive High Tone Loss Group*			
Type of Syphilis	*Subgroup A*	*Subgroup B*	*Subgroup A*	*Subgroup B*	*Subnormal Hearing Group*	*Total*
Late Congenital	0	0	0	0	5	5
Early Latent	0	0	0	1	1	2
Late Latent	1	1	1	3	6	12
Neurosyphilis	0	0	0	5	23	28
TOTAL	1	1	1	9	35	47

TABLE 9.—INCIDENCE OF IMPAIRED VESTIBULES IN NEUROSYPHILIS

	Vestibules		
Type of Neurosyphilis	*Normal*	*Abnormal*	*Total*
Asymptomatic	44	4	48
Tabes Dorsalis	24	14	38
Paresis	9	5	14
Taboparesis	3	2	5
Acute Syphilitic Meningitis	0	3	3
Primary Optic Atrophy	1	0	1
TOTAL	81	28	109

4. *Incidence in Relation to Sex and Color.* Our findings were approximately the same as noted with the hearing impairment.

5. *Incidence to Dips.* This has been discussed under analysis of hearing impairment.

6. *Relationship to Hearing Groups.* The impaired vestibules were found in 35 (62%) patients, out of 56, with subnormal hearing, in 10 (22%) patients out of 46, with excessive high tone loss;

8. *Vestibular Paradox.* We encountered 6 patients (3 late congenital syphilitics and 3 neurosyphilitics) in whom the vestibular responses were decreased to the caloric and not elicited to the rotation stimulation.

9. *Hennebert's Fistula Sign.* Hutchison's triad was found in 2 patients but we failed to detect a single fistula response in this group.

C. LABORATORY FINDINGS. *Serologic Reactions.* In our series, the diagnosis

of syphilis was originally established on the basis of positive serologic findings and clinical evidence. As the result of specific therapy received prior to our study, the reversal of the positive serologic test to negative occurred in a large number of patients. We noted the serologic reactions as follows: positive in 187 patients, negative in 117, and doubtful in 2. The positive reactions were distributed in the different forms of syphilis as follows: 38, these, 113 (43%) showed evidence of serologic abnormality, and 8 (neurosyphilitics) had shown serologic abnormality on previous occasions prior to our study. The abnormal fluids were distributed in the various types of syphilis as follows: 4 of 36 late congenital syphilitics examined, 109 of 117 neurosyphilitics examined, and none among 46 early and 64 late latents examined.

In relation to the type of hearing,

TABLE 10.—IMPAIRED VESTIBULES DISTRIBUTED ACCORDING TO AGE GROUPS

	Type of Syphilis				
Age Group	*Late Congenital*	*Early Latent*	*Late Latent*	*Neuro-Syphilis*	*Total*
0–10	1	0	0	0	1
11–20	2	0	0	1	3
21–30	0	2	1	2	5
31–40	1	0	1	4	6
41–50	1	0	4	7	12
51–60	0	0	4	12	16
61–	0	0	2	2	4
TOTAL	5	2	12	28	47

TABLE 11.—ANALYSIS OF ABNORMAL VESTIBULAR RESPONSES IN THE VARIOUS TYPES OF SYPHILIS

	Decrease to Caloric & Rotation		*No Response to Rotation Bilateral & Decreased to*		*Bilateral No Response to Caloric & Rotation*		
Type of Syphilis	*Bilateral*	*Unilateral*	*Caloric Bilateral*	**Caloric Unilateral*		*Galvanic Response*	*Total*
Late Congenital	1	0	1	2	1	3+	5
Early Latent	2	0	0	0	0	0	2
Late Latent	12	0	0	0	0	0	12
Neurosyphilis	22	2	3	0	1	1−	28
TOTAL	37	2	4	2	2	3+ & 1−	47

* In this group, the opposite vestibule did not respond to caloric stimulation.

or 69%, out of 60 latent congenital syphilitics; 27, or 55%, out of 49 early latent syphilitics; 48, or 66%, out of 80 late latent syphilitics, and 74, or 63% out of 117 neurosyphilitics. As a general rule, the positive serologic reaction is apt to be found in late congenital syphilis rather than in the late acquired forms.

Cerebrospinal Fluid. The spinal fluid was examined in 263 patients, and of the abnormal fluids occurred as follows: 47 (2 juvenile paretics and 45 neurosyphilitics) or 28%, out of 165 with normal hearing tested; 23 (1 juvenile paretic and 22 neurosyphilitics) or 51%, out of 45 with excessive high tone loss tested; and 36 (1 juvenile paretic and 35 neurosyphilitics) or 67%, out of 54 with subnormal hearing tested. Seven neurosyphilitics with a conduction loss had abnormal fluids

As a general rule, fluid abnormalities are more apt to be found in the late acquired forms than in congenital syphilis.

Comment. The existence of a syphilitic infection of the internal ear has been established beyond reasonable doubt by a correlation of the clinicohistopathologic studies and laboratory findings. Thus, the knowledge of this potentiality may aid to reach a tentative diagnosis. Nevertheless, it does not necessarily establish it unequivocally, even in the presence of a positive serologic reaction and abnormal spinal fluid. This is an obvious fact since we are concerned with a chronic process which rarely proves fatal within a short span. In consequence of this, our reliance in the clinical realm, therefore, must perforce be on the basis of statistical data fortified by the awareness of such a contingency.

On the basis of our findings, 102 patients (35%), out of 289, revealed auditory nerve involvement. A similar incidence in people without syphilis would certainly not be plausible. Among the 289 patients, 47 (16%) presented abnormal vestibular responses, and of these, only 2 patients had normal hearing. The bone conduction was normal in 2 patients with vestibular impairment, and one of these had an excessive high tone loss. Furthermore, among the 47 patients with impaired vestibules, decreased hearing and shortened bone conduction concomitant with positive serologic reaction and abnormal spinal fluid occurred in 44, or 93%. Therefore, syphilis, in our opinion, does involve the auditory nerve more frequently than any other general systemic disease.

Our findings conform to those of previous investigators[1f,18,19,29,40a] in that the incidence of impaired hearing bears a relationship to the type of syphilis of the person. Furthermore, this is substantiated by the fact that the vestibular and bone conduction impairment assumed a similar pattern as the hearing defect in its relationship to the type of syphilis.

Further, it is of interest to note that we elicited a response from the nonfunctioning vestibules of 3 late congenital syphilitics to galvanic stimulation. In spite of repeated attempts, no response was elicited from the nonfunctioning vestibules of a neurosyphilitic to galvanic stimulation. This signifies that the retrolabyrinthine part of the auditory neural mechanism was viable. On this basis, it would be indicative that the lesion in late congenital syphilis was localized to the labyrinth, while in the acquired form it was a retrolabyrinthine involvement regardless of whether the labyrinth was also included.

We did find the impaired vestibules largely occurring concomitantly with subnormal hearing in both forms of syphilis. Yet, one must take cognizance of the fact that a large percentage in the acquired class presented only cochlear involvement. In this class, presumably, the pathological process originated in the peripheral portion of the auditory nerve affecting the cochlear division as manifested during the initial phase by shortening of bone conduction with or without excessive high tone loss. Later, gradual progressive involvement of the nerve brought on a drop in the other tones. This process obviously did not conform to any specific pattern because patients showed different dips in their audiograms as noted by us and others.

The vestibular division, as a general rule, was a late victim. However, on 3 occasions, it did become involved in the early stage. In one patient, the vestibules were impaired, though the hearing and bone conduction were normal. In the later phases, apparently, the labyrinth became involved in a certain number of patients giving rise

to neurolabyrinthitis. It was most obvious that as the hearing impairment became more marked, the vestibular responses showed diminished reaction.

Our results failed to convince us that age was the sole clinical factor responsible for the hearing and bone conduction impairment, entirely independent of syphilis. One should realize that the syphilitic lesion, as a general rule, is by nature a slow progressive action. One is, therefore, subjected to the effect of age concurrently with the increasing magnitude of the syphilitic degeneration. In consequence of this, the manifestations are more apparent and greater as the decades pass by.

Lederer[41] and others[5d,22,36,37,42,44,48,51b,54,58,59,60,62,65a,72] reported that the age of onset of nerve impairment in late congenital syphilis is well beyond the period for such a child to become a mute. This fact was borne out in our series. Not one late congenital syphilitic was a mute. The earliest onset of nerve involvement was at the age of 6 years.

According to our data, the incidence of syphilitic hearing impairment in relationship to sex and race depended chiefly upon the susceptibility of the individual to neurosyphilis.

Some have reported that often shortening of bone conduction was the first sign to be detected in syphilitic nerve involvement[1c,f,5b,45]. The incidence of disproportionate shortening of bone conduction was not sufficiently significant to be labeled 'pathognomonic of syphilis'. However, it was of great importance in determining whether the auditory nerve in a syphilitic was becoming involved.

The incidence of vestibular paradox in our series was much too small for comment on its value in evaluating an inner ear impairment in a syphilitic person. As for Hennebert's fistula sign, we did not encounter a single instance in this group.

The involvement of the auditory nerve in a syphilitic person has been considered by some observers[55] as evidence of syphilis of the central nervous system, that is, symptomatic neurosyphilis. A discussion of this controversial issue is absurd if the hearing impairment in a syphilitic is considered to originate from other factors absolutely independent of syphilis.

According to our data, 70% of all hearing impairment in acquired syphilis occurred in established neurosyphilitics. Furthermore, according to Moore[51b], "Invasion of the nervous system by the treponema probably occurs in all patients with syphilis". In this connection, the fact that on many occasions the interpretation between late latent and neurosyphilis is a borderline affair should assume some significance. The difficulty arises on an arbitrary basis because so-called normal values in spinal fluid are on a variable standard.

On the foregoing basis, it is our contention that syphilitic involvement of the auditory nerve should be classified as symptomatic neurosyphilis even in the presence of normal spinal fluid. It is a noted fact that some patients with an abnormal spinal fluid eventually fall into the 'burnt-out' type. In others, the invasion probably was limited to a localized involvement of the 8th nerve without any reflection in the spinal fluid.

On the basis of the over-all picture, it is apparent that syphilis is not a frequent cause of either conduction or nerve impairment. This is an obvious deduction on the basis of the relative frequency of syphilis. However, in syphilitic persons the circumstances assume a different aspect since 25% of them develop neurosyphilis (Moore)[51b]. Of these, 60% of them, in our series,

acquired a hearing impairment. Fortunately, with the present regimen of therapy, the incidence has been reduced to between 2 and 5% showing evidence of central nervous system invasion. So, perhaps, neurosyphilis with its consequences will shortly decline to an insignificant level.

EARLY CONGENITAL SYPHILIS. Probably one of the outstanding and most satisfying results of penicillin has been the almost 100% effectiveness in its prevention of prenatal syphilis. Despite this blessing, we encountered 4 patients whose ages ranged from 8 weeks to 10 months and consisted of 1 male and 3 females. The presence of hearing was established qualitatively in each infant. The vestibular responses were normal to rotation and caloric stimulation. All were born with positive serologic reactions. In 3 of these, the reaction became normal with penicillin therapy, and the fourth infant had not yet received treatment. One spinal fluid was examined, and it was normal.

It would be presumptuous to offer our comment on this small number. However, the general impression is that it is rare to find a hearing loss in this group, and whenever it does occur, the onset is rapid and the effects devastating.

DIAGNOSIS. When confronted with a classical picture, especially between the period of late childhood and early adult life, syphilis may be assumed to be the probable cause. The presence of late stigmata is of considerable aid. A unilateral involvement should not be ignored, since it occasionally occurs. Much to our embarrassment, the usual case encountered is of insidious onset, which may not result in subjective symptoms for years.

Firstly, we must satisfy ourselves that we are dealing with a syphilitic person. A detailed family and personal history may be of great help to exclude other factors which might be responsible for the symptoms. The otorhinolaryngological examination should be thorough and include the cochlear and vestibular tests. Any granulation tissue should be biopsied and an attempt should be made to demonstrate the spirochete in an exudate by the Levaditi silver nitrate stain. If the latter two procedures fail to reveal any specificity, then despite all our efforts, the summation of the findings will simply confirm the presence of 8th nerve involvement in a syphilitic. As a consequence of this, the diagnosis is usually of necessity an inferential one, because it is based on clinical and laboratory evidence. Therefore, a careful differential diagnosis is indispensable. The disorder must be differentiated from all other diseases which may involve the labyrinth, auditory nerve, or the centers in the brain stem. This point is well-exemplified in a prior study by one of us (M. J. T.).

PENICILLIN THERAPY. Prior to the era of penicillin, reports[1f,5c,6,7,21,26,40a,49,50,60] on the efficacy of antisyphilitic therapy on inner ear lesions were controversial. Later, investigators[18,51b] concluded from audiometric studies that antisyphilitic treatment was neither beneficial nor detrimental except in acute meningeal neurosyphilis. In the latter type, the hearing impairment responded in about 50% of the patients. Recently, Lock and Tucker[43] reported their observations of the effect of penicillin in nerve deafness due to syphilis.

In the present study, we failed to observe a single patient in whom the institution of therapy, either by chemotherapy and/or penicillin, had any deleterious effect on the hearing.

Case Protocols. We are presenting case protocols from our past and present records to illustrate the response of syphilis of the ear to penicillin with special emphasis on syphilitic nerve involvement.

SYPHILIS OF THE EXTERNAL EAR. Perhaps due to its rarity, we failed to espy a primary lesion. We encountered 6 patients with secondary lesions of the external ear which were part of the skin eruption. A total dose of 4.8 millions units of penicillin was administered as 600,000 units daily. The response of the cutaneous lesions was most gratifying. Gummatous formations involved the auricle of one and the external canal of a second patient. Each received a total dosage of 10,000,000 units of penicillin given as 600,000 units daily. The gummata of the skin seemed to dissolve rapidly with complete healing occurring in less than 2 months.

SYPHILIS OF THE MIDDLE EAR. In 2 instances, patients complained of sudden loss of hearing, tinnitus, and 'sores' in the mouth. Each had developed a catarrhal otitis media associated with mucous patches involving the mouth, tongue and nasopharynx. Subsequent to a course of 6,000,000 units of penicillin given as 600,000 units daily, the rapidity of improvement and final recovery was most remarkable. In another patient the external canal was filled with pale granulation tissue and the tegmen tympani et antri was eroded by a gummatous involvement. The patient received a total dosage of 10,000,000 units of penicillin given as 600,000 units daily. It seemed to arrest further activity but roentgenographic evidence did not show any remarkable change.

SYPHILIS OF THE INNER EAR AND EIGHTH NERVE. *Late Congenital Syphilis.* Five late congenital syphilitics with defective hearing were followed from 1 to 5 years. The ages ranged from 6 to 46 years, and the duration of the hearing loss was from 2 weeks to 20 years, prior to receiving penicillin therapy. Three patients had previously received inadequate metal chemotherapy. Each patient received a total dosage of 9,000,000 units, administered in daily doses of 600,000 units, intramuscularly, for a period of 15 days. Triple typhoid vaccine was administered as an adjuvant to one patient who had bilateral interstitial keratitis. The follow-up period ranged from 1 to 3 years. In none was there any suggestion of arrest or improvement of the hearing defect. The loss continued to be progressive for both air and bone conduction. The impaired vestibules also failed to respond.

Late Latent Syphilis. Eleven late latent syphilitics were followed from 1 to 4 years. Their ages ranged from 36 to 48 years, and the duration of the hearing loss was from 2 months to 11 years. They had received various amounts of metal chemotherapy in the past and in 4 of these it was inadequate. Each received the same course of penicillin as given in the preceding group. The observation period ranged from 1 to 3 years. Prior to the commencement of penicillin therapy, the repeat audiograms demonstrated a progressive loss for high tones in each patient, and in 3 of these a subsequent involvement of the other tones. In the follow-up period, 6 patients failed to illustrate any improvement either for air or bone conduction, and 5 revealed slight gains in bone conduction which were manifested in a tardy but progressive manner. Of the 5 patients in the latter group, 2 with excessive high tone loss remained stationary, while the 3 with a loss for the entire frequency range demonstrated substantial gains. The initial improvement was in the low tones, and later, less significant gains occurred in the middle tones. Of 2 impaired vestibules, one improved appreciably.

Neurosyphilis. Twenty-three neurosyphilitics were followed from 1 to 12 years. The ages ranged from 29 to 62 years, and the duration of the hearing loss was from 1 week to 20 years. Except for 6 patients (3 acute syphilitic meningitis, 2 early asymptomatics and 1 taboparetic), each had received either adequate or inadequate amounts of metal chemotherapy prior to receiving penicillin therapy. The administration of penicillin was as previously described.

Three patients ranging in age from 31 to 37 years with an acute syphilitic meningitis developed 8th nerve impairment involving all the frequencies. The hearing loss was evaluated 7 to 10 days after the onset and monthly thereafter. At the end of the first month, all 3 patients had shown improvement: one had returned to normal hearing, the second had regained all but the high tones, and the third revealed a slight gain in all tones. The bone conduction in all 3 patients improved, but still was shortened. At the completion of the second month, the one with normal hearing sustained it, the patient with high tone loss was restored to normal hearing and the third patient made a further slight improvement for all frequencies. The bone conduction perception improved, but failed to reach the normal duration. These results were unchanged after a year's observation. The patient with a loss of hearing acuity was also left with hypoirritable vestibules, while in the other two, the impaired vestibules again became normal.

Four asymptomatic neurosyphilitics ranging in age from 29 to 49 years were followed from 1 to 3 years after receiving penicillin. An early asymptomatic patient with an excessive high tone loss and impaired bone

conduction returned to normal within 6 months. A second early asymptomatic showed a gradual progressive improvement in both air and bone conduction but did not reach the normal range after 3 years. The other 2 patients with impairments of long standing failed to show any change in hearing or vestibular defects.

Among symptomatic neurosyphilitics, 16 patients (13 tabetics, 2 paretics and 1 taboparetic) ranging in age from 30 to 62 years were followed from 1 to 3 years subsequent to penicillin therapy. Three of the patients were subjected to artificial fever therapy as an adjuvant to penicillin therapy. No improvement was detected in the hearing loss, bone conduction impairment or vestibular disturbances.

Comment. There is conclusive evidence that penicillin is more effective in the treatment of syphilitic nerve deafness than any previously described treatment. Despite this fact, the value of penicillin for inner ear involvement in early or late congenital syphilis is questionable, because it is unsuccessful even in arresting the progress of the impairment in late congenital syphilis. Whether it may eventually prove to prevent an inner ear involvement, cannot be ascertained at present. A late congenital syphilitic followed by Loch and Tucker[43] for 731 days showed a progressive loss of hearing.

Our present meager available data indicate that penicillin has decidedly reduced the incidence of abnormal spinal fluids in early and early latent syphilis. Striking in our study is the fact that not a single patient with early or early latent syphilis, who had received penicillin at an early stage of the infection, developed an 8th nerve involvement.

As concerns 8th nerve involvement in late or late latent syphilis, it is of interest to note that, whereas all prior methods of treatment had failed to exert any influence, penicillin therapy accomplished results by either improving or arresting the impairment.

Similar evidence was observed in early asymptomatic neurosyphilis, while in late asymptomatic or symptomatic neurosyphilis (except for acute syphilitic meningitis), the clinical results were the same as in the pre-penicillin era. The hearing loss in our 3 patients with acute syphilitic meningitis responded in a similar manner as reported by Loch and Tucker[43]. Penicillin is not only safer but a more effective agent than the heavy metals in restoring to normal or greatly improving 8th nerve involvement accompanying acute syphilitic meningitis.

Summary and Conclusions. A clinicostatistical analysis of the results obtained in the study of the otologic findings of 310 patients with an established diagnosis of syphilis is reported. This group consisted of random samplings of each type of syphilis of both sexes in each age group. The patients were consecutive except for those who were eliminated because their hearing loss anteceded the acquisition of syphilis. The higher incidence of males and colored patients was due to chance.

The procedure adopted for evaluating the cochlear and vestibular functions is given. On the basis of stated criteria, the hearing acuity of the patient is classified into definite hearing groups. In the case of a marked hearing difference for both ears, the classification is based on the poorer one. The vestibular responses are noted as normal or impaired since any doubtful dysfunction was considered with the normal ones.

The required criteria for a clinical diagnosis of syphilis of the 8th cranial nerve, symptomatology and laboratory findings are given to indicate that their importance in evaluating an inner ear involvement in a syphilitic person is limited. As a general rule, bacteriologic and histopathologic aid is not feasible. In consequence of this, our trust, from a clinical aspect, has no other option

than to be influenced by statistical data.

On the basis of the foregoing, special emphasis is laid upon the methodical analysis used in ascertaining the interrelationship between the hearing groups and vestibular responses and the various factors which may have influenced them.

By correlating the incidence of hearing impairment and of vestibular disturbance, our evidence shows that the general incidence of inner ear involvement in syphilitic persons is higher than in those of the same age, sex and color without the disease. Apparently, age was not the sole clinical factor which determined the degree of hearing impairment, vestibular dysfunction or shortening of bone conduction in our patients absolutely independent of syphilis. It appears that the only association sex and race have with the incidence of syphilis of the inner ear depends chiefly upon the susceptibility of the individual to neurosyphilis.

An analysis of our data shows the incidence of inner ear disease to be highest in neurosyphilis, especially the symptomatic form. Prior reports concerning a relationship between the incidence of syphilis of the inner ear and the type of syphilis affecting the person are thus confirmed. Furthermore, of significance is the evidence indicating that the syphilitic lesion in the late congenital type is apparently localized to the labyrinth, while in the acquired form it appears to be a retrolabyrinthine involvement regardless of whether the labyrinth is also included.

On the basis of our results, we feel that it is reasonable to accept disproportionate shortening of bone conduction as a significant sign in evaluating syphilitic involvement of the 8th nerve. Evidence is presented to support the contention that syphilitic infection of the auditory nerve should be considered as symptomatic neurosyphilis. An analysis of the hearing defects indicates that there is no special form of nerve impairment which may be regarded as pathognomonic of syphilis.

In the acquired form of syphilis, the vestibular involvement rarely antedates the cochlear impairment. Of significance is the fact that, generally, as the hearing impairment becomes more marked the vestibular responses show diminished irritability.

It is reasonable to assume from the over-all picture that syphilis is not a frequent cause of either conductive or nerve impairment. Generally, the diagnosis is an inferential one and, therefore, a careful differential diagnosis is essential.

Case protocols are presented to illustrate the response of syphilis of the ear to penicillin therapy with special emphasis on syphilis of the inner ear and 8th nerve.

Penicillin has no deleterious effect on normal or impaired hearing.

Evidence is presented that penicillin is more effective in the treatment of syphilitic nerve impairment in late and late latent syphilis and early asymptomatic neurosyphilis than any previously described method.

In contrast, evidence is presented that no arrest or improvement of inner ear involvement is effected in late congenital syphilis.

There is evidence indicating that no clinical gain has been achieved in treating syphilis of the 8th nerve in late asymptomatic and symptomatic neurosyphilis with penicillin, except for acute syphilitic meningitis which responds most notably.

Analysis of our data shows that early and adequate penicillin therapy in early and early latent syphilis prevents 8th nerve infection. Probably one of

the outstanding and most satisfying results of penicillin is the almost 100% effectiveness in its prevention of prenatal syphilis.

All evidence indicates that syphilis of the inner ear and 8th nerve will in the near future decline to an insignificant level with the help of penicillin.

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WEBER-CHRISTIAN SYNDROME

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ADIPOSE tissue, long a neglected field for study[91], has recently been the subject of much interest to internists, dermatologists and pathologists alike. The multiplicity and complexity of disease states involving the fat have led to a large number of publications, but no really comprehensive correlation of the morphology, biology and pathology of adipose tissue has appeared until the recent works of Baumgartner and Riva[10], Smetana and Bernhard[80], as well as Blanc[16]. Blanc's comprehensive monograph not only reports the studies of the pathogenesis of liponecrosis but correlates the clinical and pathologic aspects of the problem and describes two new processes. It is my purpose in this review to outline briefly the general field of fat necroses, and to delineate in some detail the features of one particular type which is presently of interest to internists and dermatologists, namely, relapsing nodular non-suppurative panniculitis, the so-called Weber-Christian syndrome.

FAT NECROSIS. According to Blanc the adipose tissue which represents 18% of the body weight of a normal adult is distributed in accordance with a definitely strict pattern. Racial and hormonal factors and probably nervous and vascular regulatory mechanisms control the fat and it plays a role in alimentary reserve and affords thermal and mechanical protection. For the understanding of the pathogenesis of certain disturbances of the fat, it is necessary to recall the structure of adipose tissue. Aside from the fat cells, the spaces between the lobules and their vascularization are important in the pathology of the diseases under consideration. Wells[91], and Blanc[16] have detailed the arrangement of the abundant blood supply of fat. Each lobule is assured its independence by an ar-

tery and two veins. In addition, there are capillaries and collateral circulation. This blood supply explains the ease with which certain areas (for example, periorbital) develop edema. In fact, this anatomical characteristic has been invoked in the explanation of exophthalmos of hormonal origin. The composition of fat in a particular region is relatively constant under given circumstances. The exact details are not germane to this discussion.

The development of necrosis of the fat is marked by a reaction to the products of disintegration, followed by a stage of restitution. The facility of restitution depends upon the extent of the necrosis, upon the intensity of the reaction to the products developed on the spot or to their more or less easy local elimination. The nature of the necrotic mass and the terrain also determine the type of reaction. Age, fibroblastic activity, general disease (agranulocytosis, leukemia), the development of inflammatory infiltrate and predisposition condition the development of the reaction. Thus fat necrosis is a combination of a special local and general terrain and complex responses to a variety of irritants. In healthy individuals, fats are destroyed, utilized, assimilated and synthesized without any of the intermediate products of their disintegration or of their synthesis causing disease. Since the split products are free from observable action, the changes are in all probability intracellular.

When the necrotic mass ulcerates, some fatty substances are released into the intercellular spaces and abnormal cellular reactions of enzymatic and chemical character are initiated. There is also a change in the intercellular fluid. A series of successive changes (oxidation or saponification) yield products of foreign character or normal substances in abnormal quantities or abnormal physical state. Localized alteration of membrane permeability facilitates exchanges between the cell and the environment. A number of different agents induce the development of steatonecrosis. However, since the histology produced is so complex, one cannot designate the precise role of a given factor in a particular reaction. The necrosis may be initiated by chemical and physical agents (cold, heat, mechanical factors, such as compression, or distention, trauma). According to Blanc, a number of cell types are found in the foci of fat necrosis.

Adipose tissue is extremely fragile. Feeble irritants, physical or chemical, slight trauma, such as wounds, surgical or otherwise, may provoke the lesions. In spite of their frequent occurrence, fresh necroses are rarely seen in the human. The discrete lesions pass unnoticed and the massive lesions show developmental phases or some scarring. The initial stages of the lesions have been determined in detail experimentally. It is interesting to note in connection with the Weber-Christian syndrome that the first cells to appear in most of the reported cases, are lymphocytes and monocytes (polymorphonuclear cells, c.f. Ungar[85], Lever[54]). These cells contain the most lipase. Each focus of necrosis is surrounded by lymphocytes, plasmacytes and histiocytes. In the mild necrosis of the connective tissue, these cells (lymphocytes and some granulocytes) exercise a lytic action on the necrotic tissue. There seems to be but little phagocytosis of the elastic tissue debris. In brief, the first phase of the necrosis is a relatively simple phenomenon. Dead cells are invaded by the lipophagic histiocytes which seem little by little to metabolize the fat. The lipophages phagocytize almost all of the fat but one can find small quantities in the intercellular spaces. Secondary degen-

eration of the wandering histiocytes accounts for the intercellular fat. The released fat acts at first as a foreign body. Necrosis of fat tissue is remarkable for its tendency to chronicity, extension, and the development of fibrosis. The specific reaction of fat tissue is related to its chemical composition. Various agents will have an identical effect. Regardless of the case (traumatic, chemical or microbic) the pathogenesis is the same. If the necrosis of fat is moderate, the proliferation of fibroblasts results in a discrete scar. If the necrosis is extensive but develops slowly, the fibrosis can be rather important. The fibrosis is accompanied by the deposition of hemosiderin from hemorrhage. On the other hand, certain of the fat necroses are associated with atrophy. Thus the lipodystrophies from insulin may be classed as a type of post-inflammatory atrophy of the fat. One may rarely encounter localized hypertrophy at the point of insulin injection. This represents an exaggerated regeneration following necrosis.

Although the presence of irritating bodies and substances may explain the slowly developing local lesion, their presence does not account for the progression of the lesions. Blanc lists the following possible modes as spread: a) transport by histiocytes of toxic lipids or irritants in the tissues adjoining the necrosis or in the regional lymph nodes, b) direct lymphatic transport of soluble fat, c) local persistence of toxic factors (products of disintegration of endogenous fat, hydrocarbons, heavy metal) provoked by diffusion of new necroses. (This induces a chain reaction). d) Another vicious cycle is from vascular lesions. (The obliteration of the vessels provokes secondary necrosis). e) Pathologic lipids alone can give rise to the appearance of reactions. (A local or general abnormality of fat metabolism can be the cause). f) The lymph nodes play an important role in the special form of sclerosis described by Blanc in 1947, "l'adénoliposclérose dysprotéinique" (c.f. lipodystrophie intestinale of Whipple.) g) Presence of a pathologic protein may cause a number of cases (permanent or transient dysprotidemie).

In the general concept of liponecrosis, the matter of cellulitis or fibrositis has been described. Copeman[26] defined cellulitis or fibrositis as a painful (rheumatismal) affection due to disturbance in the permeability of the cell membranes. Later authorities have called this cellulitis or fibrositis, panniculitis, a process to be differentiated from the Weber-Christian syndrome (see below). Lipogranuloma is reserved for lesions which are in reality granulomas with prominent cellular infiltrate (see below).

Classification of the various types of fat necrosis have also been presented by Abrikossoff[1] and later by Baumgartner and Riva[10]. While these classifications are useful clinical schemes, the basic pathologic reaction of the fat in all the processes is the same. The cause is the only variable. The classifications do not indicate the mode of evolution. Blanc[16] claims that each lesion whether isolated or whether part of a syndrome is "susceptible" of being transformed. Blanc describes it as "stéatonécrose microkystique" a characteristic picture through which all fat necrosis lesions pass. Microscopically, the tissue presents a "Swiss cheese" appearance. The fat may be normal or a little altered and contains microcysts. The interlobular septa are thickened. Between the microcysts one may see foam cells (lipophagic). The picture may resemble tuberculosis or sarcoid. Blanc also calls attention to microcysts "en pelure d'oignon" in which the cav-

ities are lined by a series of lamellations resembling the layers of an onion. The pathologic picture corresponds to that seen in paraffinoma experimentally produced or occurring in humans. Some of the cysts may contain calcium. Other types described are "liposclérose microkystique simple", "liposclérose alveolaire"; "liposclérose cicatricielle massive"; "liposclérose perikystique"; "Kystes par stéatonécrose". Based on his studies and the literature, Blanc submits the following classification. It has the advantage of listing not only the various types of liponecrosis, but also the factors determining their development.

"Stéatonécroses discrètes.
Stéatonécroses microkystiques.
Stéatonécroses disséminées
Syndrome de Rothmann-Makai.
Syndrome de Weber-Christian.
Kystes par stéatonécrose.
Liposcléroses massives chéloïdiennes.
Formes progressives sous l'action de facteurs locaux.
Formes progressives sous l'action de facteurs généraux:
1. Liposclérose nodulaire dysprotéinique.
Liposclérose prévértebrale dysprotéinique:
a) médiastinale,
b) rétropéritonéale."

Baumgartner and Riva suggest the following classification for the non-purulent non-specific circumscribed panniculitis:

A. Panniculitis as secondary reaction of the fat tissue on processes in the neighborhood which may be inflammations but also malignant tumors.
B. Artificial panniculitis caused by external factors.
1) Subcutaneous injection with oil (oleogranulomas), paraffin (paraffinomas), physiological salt solution (Schwarzman) insuline (insulin - dystrophie and insulin-lipomas), and others.
2) Local mechanical traumata, for example, in the mamma where differentiation from a malignant tumor may be difficult; adiponecrosis subcutanea neonatorum.

In this group, as well as in the following group C, a constitutional predisposition is probably an important factor.

C. "Spontaneous" circumscribed panniculitis, a group in which two syndromes may be distinguished:
1) Weber-Christian's disease or syndrome,
2) A group or syndrome, called by Baumgartner and Riva "Spontaneous panniculitis of Rothmann-Makai."

According to Baumgartner and Riva it is impossible to distinguish the various types of panniculitis by means of the histological picture alone, probably with exception of adiponecrosis subcutanea neonatorum wherein crystals are found. The only differences between the two syndromes in group C are clinical. Cases of spontaneous panniculitis which do not fulfill the clinical criteria of Weber-Christian's syndrome are classified by Baumgartner and Riva in group C2 which is certainly very heterogeneous. Kooij[50] suggests, the extension of Group B of Baumgartner and Riva's classification to all cases of primary non-specific panniculitis of known origin and thus to add 2 subgroups:

D. Panniculitis caused by known chemicals, especially medicines (bromides and iodides).
E. Panniculitis caused by infection, either specific or non-specific. It is known, that tuberculosis, syphilis, sporotrichosis, leprosy, and others

cause non-specific inflammatory processes in the subcutaneous tissue.

These panniculitides with a varied infectious origin have the same histological structure. As long as a definite cause has not been ascertained, it is better to leave the diagnosis in suspense and to bring the case provisionally under Group C. The differentiation by Baumgartner and Riva between the syndrome of Weber-Christian and that of Rothmann-Makai seems to be still premature and artificial. In (spontaneous) panniculitis the constitutional component is probably of paramount importance, and possibly the clinical differences between the syndromes of Weber-Christian and Rothmann-Makai are merely expressions of different grades of reaction. At the best, one can speak of the Weber-Christian type of panniculitis. This type must be considered as a clinical variant of the larger group of spontaneous panniculitis until we know more about the etiology and pathogenesis.

As a second clinical variant of spontaneous panniculitis the non-tuberculous form of erythema induratum (Bazin) could be accepted. Montgomery, O'Leary and Barker[58] have described this condition as "nodular vasculitis," but according to Kooij, "erythema induratum non tuberculosum" seems the better name. The condition is characterized by painful nodules on the calves of 30 to 40-year old women, which seldom ulcerate and which in most cases remain for a shorter period than in erythema induratum (Bazin), although many relapses are the rule. Histologically, there are different grades of vasculitis and of panniculitis with foreign body giant cells and atrophy of the fat, without typical tuberculoid structure. Histologically, there is little difference from spontaneous panniculitis. At best the vascular changes are more intensive. Sometimes the tuberculous form of erythema induratum histologically resembles common panniculitis. This form belongs to Group B. The sarcoids of Darier-Roussy might be considered as a third clinical variant of spontaneous panniculitis as far as they resemble histologically a non-specific panniculitis of which the etiology is not known.

There are certain general clinical characteristics of all the forms of fat necrosis. All the lesions have a latent period before they become clinically manifest. The duration of the latent period depends upon the depth of the lesions, on the thickness of the panniculus adiposus and on the degree of inflammatory reaction. This is of great importance in investigation of the relation of trauma to the lesion which may appear some months later. It can always be considered spontaneous fat necrosis. The obese, especially women, are affected. The nodules are hard and palpable beneath the skin, some feel "scirrhous." Their size has been described as varying from a "lentil to an orange." The early lesions are sharply delimited but infiltration is a dominant trait of certain progressive liposcleroses. They are for the most part, movable under the skin, but the nodules can adhere to the fascia, the subadjacent muscles or even to the skin. The skin may be red, tender, brilliant, depending upon the stage of inflammation. At times, the skin may have an orange peel appearance. Ulceration with evacuation of the contents of a cyst is rare. When this occurs, the liquid is grumous or fatty (c.f. Shaffer[77] below). The mass can be strictly local but lymph node hyperplasia is not rare, a feature suggesting metastasis. The nodules are symmetrical (arms, breasts and thighs) appearing in general insidiously, without pain and often rapidly within several hours. Palpation may induce pain and Roentgen-ray examination may reveal the presence

of calcium. Deep (mediastinal or retroperitoneal) fat necrosis is difficult to diagnose: pseudotumors. Fat necrosis of the soft bones likewise poses a difficult diagnostic problem. Blood changes are not characteristic enough to allow definite conclusions.

Before describing the Weber-Christian syndrome, it is pertinent to note a few of the excellent summaries which have appeared in recent years. Among these are those of Bailey[8], Shaffer[77], Larkin and colleagues[52], Miller and Kritzler[56], Gay Prieto[35] and colleagues, Bendel[12], Hallahan and Klein[38], Shuman[78], Kooij[50], to mention only a few. Specific reference to other sources of pertinent information will be alluded to in the text.

DEFINITION OF THE WEBER-CHRISTIAN SYNDROME. Although this process is often referred to as the Weber-Christian syndrome or disease, actually the first case showing the features of this process was described in 1892 by Victor Pfeifer[65] and a similar process was described by Gilchrist and Ketron[37] in 1916 and one that might be a late phase of the same process was described in 1918 by Sundwall[82] under the title of "Localized Areas of Atrophy or Fat in Derma or Subcutaneous Tissue." Credit for the recognition of this process as a separate entity goes to Weber[88] who originally described it as "a case of relapsing non-suppurative nodular panniculitis showing phagocytosis of subcutaneous fat cells by macrophages." Subsequently attention was called to the syndrome by Christian[24], who altered the name by the insertion of the word "febrile." Since this original group of cases was described, numerous others have been added to the world literature. However, it might be said parenthetically that the designation of cases by a particular case number is erroneous, since even in the most carefully compiled summaries reported, cases have been omitted for various reasons. In addition, there are cases which have not been reported because the process is considered commonplace, even though the actual number of both reported and unreported cases must be fewer than 100.

In spite of the etymology of the designation panniculitis, there is a disagreement as to what should be included in the panniculitis concept. For example, Baker[9], states that Copeman and his associates should be given credit for focusing attention on the various syndromes which come under the heading of non-articular rheumatism. Panniculitis, to be clearly distinguished from the skin disease of that name, is one such syndrome which is commonly overlooked. However, the inclusion of the so-called Weber-Christian syndrome in the panniculitis group need not necessarily be incorrect since, as will be shown later, there may be a relationship between panniculitis and the collagen diseases. Undoubtedly, a number of cases of Weber-Christian syndrome are buried under a variety of other titles, which will be mentioned later as synonyms for this disease, but particularly, for example, under the term lipogranulomatosis which the Germans used for this process. Gay Prieto and his coworkers feel that the proper name should be "Pfeifer-Weber-Christian syndrome." All of the cases of this syndrome have one feature in common, that is, involvement of the subcutaneous or visceral fat. Panniculitis may also represent, as previously indicated, a secondary feature of many other processes or may play a minor role in other processes. The coincidence of polydermatomyositis and panniculitis, as reported by Weber and Gray[90], indicates that the muscles may also be involved. The matter of suppurative or non-suppurative features has also

come in for a certain amount of discussion. Bendel, for example, leaves out the non-suppurative phrase, as part of the name because several cases have shown frank pus (Ungar[85] and in another case Weber)[89], or greenish yellow material (Blinkley[14], Ives[41], Shaffer[77]). The material from all these lesions was sterile.

Keil[45] from his attempt to classify the various types of panniculitis concluded that "primary panniculitis" should refer to the condition in which changes occur in the adipose tissue over wide stretches of the body, but no suppuration is present. There are two forms: 1) the febrile and 2) the afebrile. The febrile form is characterized by crop-like outbreaks of markedly tender subcutaneous nodules on the extremities associated with prolonged, irregular fever and constitutional symptoms. The nodules undergo involution leaving atrophy of the adipose tissues and dimpling of the skin. Cultures of the blood are sterile. The afebrile form shows a massive painless induration of the subcutaneous tissue of the anterior aspect of the trunk, the overlying skin being uninvolved. Keil states that panniculitis may occur coincidently with erythema nodosum, nodular erythema due to a drug, erythema induratum, Darier-Roussy sarcoid, lipogranuloma and dermatomyositis.

Moore[59] believes that the disorder in adults is the same disease as subcutaneous fat necrosis of the newborn. In the latter process it is assumed that an obstetrical trauma acting on fats with a high melting point, which is present in the newborn, is responsible for the condition (65% oleic acid, as compared with 86% in adult fat; the difference is made up by fats, such as palmitic acid, with higher melting points). On the other hand, the children's disease is afebrile, the blood lipids and all the fractions are increased, the iodine number is decreased with reversion to normal values on recovery. There are no residual depressed areas at the sites of lesions in the children's disease. Duran-Reynals[29] has described a similar disease occurring in rabbits which consists of necrotising disease affecting the fatty and muscular tissues. In 1908, Berner[13] described a peculiar case with multiple partly ulcerative subcutaneous inflammation of the fatty tissue in a patient with a large pancreatic tumor. Ayres[7], in 1946, also described a patient with liquefying features.

Numerous names have been applied to this fat necrosis in patients whose symptoms were similar to those now known as those of the Weber-Christian syndrome: ischemic fat necrosis, saponifying necrosis, necrosis of the subcutaneous fat tissue, lipophage granuloma, lipophagic granuloma, lipogranuloma, lipodystrophy, adipose necrosis, lipoid necrobiosis, cystosteato necrosis. Smetana and Bernhard[80] have described patients under the name "sclerosing lipogranuloma", which includes the Weber-Christian syndrome type of fat necrosis. On the whole, however, most of the cases in this report deal with a local reactive process following injury to adipose tissue.

Although certain details of the clinical picture of the Weber-Christian syndrome will be given later, for purposes of definition, the clinical characteristics of this process as described by Bailey[8] are: 1) recurrent attacks of malaise and fever, of widely varying degrees, accompanied by subcutaneous nodules; 2) predominant occurrence of the condition in adult women; 3) localization of the subcutaneous nodules on the trunk or extremities, but mainly on the thighs; and 4) the tendency to subcutaneous atrophy with its resultant depression at the site of involution. The histologic features consist of 1) edema and necrosis, primarily involv-

ing the subcutaneous fat; 2) diffuse appearance of cells phagocytic for fat, with a few multinucleated cells; 3) very limited fibroblastic stimulation; 4) notable absence of epithelioid nodules; 5) infrequent, severe vascular changes; and 6) primary involvement of the entire fat lobule.

Incidence. As previously mentioned, any attempt to estimate accurately the number of cases of the Weber-Christian syndrome which have been observed ends in a state of inaccuracy, because many of the patients have not had their cases reported and certain summaries, for varying reasons, do not include some of the reported cases. The article by Bendel, one of the outstanding compilations of recent years, includes information on 44 cases. The following additional cases have come to our attention in the available recent literature: Machacek[55] (4 cases); Bunnell and Levy[20]; Kennedy and Murphy [47] (3 cases); Arandes[4]; Lever[54]; Mostofi and Engelman[60]; Johnson and Plice[42]; Rubin and Bland[73], (2 cases); Brudno [19]; Gertler[36]; Jones, Lamb and Goldman[43]; Frost[34]; Prevost and Leger[69]; Muri[61]; Kooij[50]; Bjornstad[15]; Hallahan and Klein[38]; Caccialanza[21]; Sanford *et al.*[75]; Pierini and Pompotsiello[67]; Orfuss[64]; Koch[49]; Gay Prieto *et al.*[35]; Hanrahan *et al.*[39] (2 cases); Drew *et al.*[28]; Shuman[78]; Carache[22]; Kinmont[48]; Samitz and Coletti[74]; Schwartz, Loftus and Fishler[76]; and Eisaman and Schneider[31]. In spite of the apparent increase in number of cases of the Weber-Christian syndrome recently reported, it is not possible to say anything definite about the actual cause of this process. The new cases, however, have provided considerable information on the geographic distribution of the process, and in some instances there have been positive additions to our knowledge of the pathology of this process. The Weber-Christian syndrome as indicated by all those reported cases is most commonly found in obese women, between the second and fourth decades of life. The youngest case reported was in a 6-months-old child (Carol, Prakken and van Zwijndregt[23]) and the oldest was in a woman of 70 (Sweitzer[83]). Although this syndrome has been said to occur in about three times as many females as males, more recent cases suggest a more equal distribution between males and females. The Weber-Christian syndrome has been reported in individuals from a number of countries: Chinese, Germans, Spaniards, Scandinavians, Syrians, British, South Americans, Filipinos, Australians, Canadians, Hawaiians and of course residents of the United States. It is generally stated that Negroes are not affected by this process, but we have found records of 3 such cases (Johnson and Plice[42]; Samitz and Coletti[74]; and Machacek[55]). There appears to be no obvious relationship between occupation or state of nutrition and the occurrence of relapsing febrile nodular non-suppurative panniculitis. It is unassociated with any other specific disease. There is no evidence that it is a contagious process since no epidemics have been observed, nor have more than one member of the same family been affected.

Etiology. The cause of relapsing febrile nodular non-suppurative panniculitis is not known. Numerous etiologic agents and circumstances have been supposed to cause individual cases. These are outlined briefly.

HALOGEN COMPOUNDS: IODIDES AND BROMIDES. Although Weber's[89] second case as well as Rosenberg and Cohen's[72] 2 cases showed the onset of a relapse coming after administration of halogens (appearance of fresh nodules and a rise in temperature which could be produced at will by the administration of a halogen, the reaction as

promptly disappearing on discontinued medication), the actual role of the halogen compound is not definitely proven. Keil[45] believes that these halogen compounds do cause this particular type of panniculitis. Bailey[8] felt that iodide therapy was a possible cause in 4 of his cases. He too, noted exacerbation of crops of nodules after the readministration of iodine in 3 patients. Niedermayer and Moran[63] associated a definite remission of symptoms when the use of iodine containing drugs such as, iodides and iodized salt was discontinued. The application of iodine to the skin of sensitive individuals, according to Larsen and Ootkin[53], produced a picture histologically resembling that of relapsing febrile non-suppurative panniculitis. The same response was reproduced by the subcutaneous injection of camphor in oil, insulin and paraffin. Shaffer attempted, unsuccessfully, to produce an exacerbation of the lesions in his case of liquefying nodular panniculitis by the administration of potassium bromide and potassium iodide. The same relationship or lack of relationship to the halogen compounds with exacerbation of Weber-Christian disease has been noted by more recent authors. For example, Baumgartner's patient had a flareup following the administration of potassium iodide. On the other hand, there was no halogen factor in the cause of the 3 cases reported by Schwartz and his colleagues in 1952. In Eisaman and Schneider's case there was a history of venogram with 40 cc. of 70% iodopyracet injection (Diodrast).

Although other drugs have been mentioned in the case report of patients who subsequently develop the Weber-Christian syndrome, the mere history of drug ingestion is not tantamount to the incrimination of that drug or drugs as the cause of the preceding development of the Weber-Christian syndrome[11]. Such a case in point is that of Mostofi and Engleman[60] whose patient had received quinacrine hydrochloride, quinine, sulfadiazine, penicillin and antimony sometime during the preceding few months before the onset of fatal relapsing febrile non-suppurative panniculitis. Likewise in Bunnell and Levy's[20] case, the relationship of the disease to long administration of sulfonamides (sulfamerazine, sulfathiazole, sulfadiazine) and penicillin was questioned.

INFECTIOUS AGENTS. In spite of an intensive search by a number of authors reporting cases of Weber-Christian's syndrome, no organism has been demonstrated consistently to be the cause of this process. Occasional cases, however, such as those of Alderson and Way[2], may show organisms which appear to initiate the disease. Studies involving urine and blood cultures and various agglutination tests for a number of organisms, cultures of involved skin lesions, animal inoculation of extracts of skin lesions, cultures for anaerobic and aerobic bacteria, ameba, and tubercle bacilli have all yielded negative or inconclusive results. Cutaneous tests for tuberculosis, coccidioidomycosis and trichinosis, tests with staphylococcic and streptococcic toxins, stool cultures and examinations of blood and spinal fluid tests as well as examinations for animal parasites, have all yielded negative results. In spite of these negative results, there are a number of studies suggesting that if the process is not due to an actual infection with bacteria, it might represent bacterial allergy. For example, Arnold's[5] patient whose lesions responded to sulfapyridine is one in point. Likewise, the previous report by Skiöld[79], of a patient who had a flareup of lesions after removal of 14 infected teeth, suggests a bacterial cause. Fur-

thermore, Ives[41] reported a case of possible Weber-Christian syndrome in which the cause was attributed to an organism entering through a lesion in the hand. Schwartz, Loftus and Fishler[76] found hemolytic streptococci on throat culture in one case, and in another case colon bacilli grew out of the urine. Their third case, the most severe, showed no organisms. Shuman[78] obtained cultures from the open incision of a lesion which contained a few *Staphylococcus pyogenes var. aureus* coagulase-positive organisms. However, numerous other microbiologic studies yielded negative results. Sanford and his coworkers[75] also believed the cause of this process was bacterial. They recovered Gram-positive cocci chains from (*Streptococcus viridans*, aerobic and anaerobic organisms were slightly sensitive to streptomycin and moderately to penicillin and strongly sensitive to chloramphenicol and aureomycin). Blood cultures, however, gave negative results. This case and others which have responded to the antibiotics lend further support to this thesis of potential bacterial cause. Other cases reported to have a bacterial background were the 2 patients of Ungar and Friedman[85] in whom the process was thought to be due to a bacteremia with *S. hemolyticus and S. pyogenes var. aureus* respectively. Puente[70] of Uruguay also has reported organisms in the nodules. Netherton[62] believed that the local lesions were the result of blood-borne chemicals and bacteria. He felt that the nodules were really metastatic lesions.

Some authors believe that certain of the cases were due to tuberculosis. For example, Carol, Prakken and van Zwijndregt[23] felt that tuberculosis was a factor in their 2 cases and suggested further that relapsing febrile nodular non-suppurative panniculitis might be an acute or subacute form of Darier-Roussy's sarcoid. This form of sarcoid, however, does not show such periods of remission as does panniculitis. Tilden and his coworkers[84] found extensive tuberculosis at the necropsy of a patient with typical cutaneous manifestations of the Weber-Christian syndrome. In this case, there was no demonstrable relationship between the 2 processes. Pierini and his colleagues[66] noted that 2 individuals among their 4 cases had tuberculosis. These authors noted a similarity of relapsing febrile non-suppurative panniculitis to macronodular indurative tuberculosis.

Focal infection has also been considered as a possible background for this process. One of Pierini's 4 patients seemed to have recovered after removal of septic tonsils. Bailey noted dental and tonsillar disease in several of his cases. Others, incuding the original decription by Pfeifer, indicated the possibility of associated dental infection. On the other hand, a number of authors, including Larkin, DeSanctis and Margulis[52], observed that foci of infection may be removed with no apparent change in the course of this process. Miller and Kritzler's[56] patient, who died apparently of Weber-Christian syndrome, showed no demonstrable foci of infection. Likewise the fatal case of Mostofi and Engleman[60] was free from foci of infection. Just as there are cases with associated dental and other foci of infection, there are patients in whom similarly no demonstrable foci are present.

Shaffer[77] attempted to demonstrate the presence of viruses in his patients with liquefying panniculitis by the use of a Berkefeld filtrate of the aspirated contents of an early lesion. This produced no reaction when injected intracutaneously or subcutaneously.

OTHER POSSIBLE CAUSES. Among the causes given for a number of cases are

a variety of conditions, such as renal failure, dietary deficiency, impaired fat metabolism, foreign body reaction, endocrine disturbances, hematologic changes, changes in blood chemistry, associated neurovascular dystrophy, trauma, allergy and disturbance of the collagen. Since many of these factors are only present in occasional cases, special note will be made of a few which seem to have affected more than one patient or in a few which seem to have reasonable potentialities for being at the basis of the Weber-Christian syndrome. Trauma has been suspected of being a factor in a number of individuals. Binkley[14] observed that his patients bruised easily. Baumgartner and Riva[10] found that one patient, affected with panniculitis during a relapse, developed a characteristic local panniculitis on slight trauma. Fraser's[32] woman with Weber-Christian syndrome developed typical nodules within 2 or 3 weeks after an area had been traumatized. Brill[18], as well as Shuman, and Miller and Kritzler noted the occurrence of nodules after trauma. Ives[41] obtained a history from his patient that an ulcer had developed on the arm from a cigarette burn sometime before the onset of the process.

There have been no consistent chemical changes in the blood in spite of the numerous studies involving blood sugar, blood chloride, protein, cholesterol esters, nitrogen, creatinine, phosphorus, calcium, total lipids, fatty acids, lipase, phospholipid, phosphotase, uric acid, bromide and iodine. In this connection, it is interesting to note that Machacek reported 4 patients with diabetes and the Weber-Christian syndrome. Gay Prieto and his colleagues' case was a child of a diabetic father.

Liver function studies were normal in several cases, in spite of the fact that several of the fatal cases showed liver damage. Hematologic changes are interesting in that, although leukopenia occurs in many cases, the leukocyte count may be normal or increased during an exacerbation of the panniculitis. Nothing consistent has been noted in the differential white count, nor is the variation of the red cell count of any particular significance. Several good compilations of the interesting details of the hematologic findings are available[12,38].

Of interest, in connection with the possible cause of this process, is the attempt by some authors to relate it to the collagen diseases. Although Weber had previously observed a patient with the Weber-Christian syndrome and dermatomyositis, Kennedy and Murphy[47], in 1949, also suggested a relationship between this process and dermatomyositis. Brudno[19] felt that his patient's suggestive nodular panniculitis (Weber-Christian syndrome) was allied to the group of collagen diseases. This is a reversion, in a way, to the relationship of panniculitis to rheumatism, claimed by Stockman as well as by Weber. The relationship of the endocrine glands to the Weber-Christian syndrome has not been established.

Pathology. The microscopic changes in the lesions of the Weber-Christian syndrome were originally described by Pfeifer[65] as confluent crops of minute inflammatory foci in the subcutaneous tissue, appearing concurrently with the generalized manifestations of the disease. Christian described these histopathological changes, confirmed by subsequent authors, as basically consisting of the following findings: The interstices of the adipose tissue are more or less heavily infiltrated with leukocytes of various types, with separation and partial to complete reabsorption of fat cells; serous atrophy even necrosis of fat have been ob-

served. Lipophagocytosis by macrophages is sometimes prominent. The reacting leukocytes consist of lymphocytes, plasmacytes, cells of the monocyte-macrophage series and a sparse interspersion of neutrophiles and eosinophiles. Multinucleated giants cells are occasionally encountered. There is also proliferation of local fibroblasts and reticulum cells. The inflammatory process is singularly limited to the fat lobules proper, intervening fibrous septa and trabeculae being spared. Changes in the blood vessels are usually slight and limited to periarteritis and endarteritis. Other vessel changes, such as intimal thickening of vessels, occasionally with obliteration of the lumen and recanalization, were found by Niedermayer and Moran as well as by Arnold. Cummings and Lever emphasized increased vascularity of inflamed fat with lamellation of the vessel walls. While Alderson and Way[2] noted the absence of hemorrhage and pigment deposition, Bunnell and Levy noted hemorrhage in the early lesions and focal areas of brown pigmentation. Christian observed no fatty crystals, but Bunnell and Levy observed crystalline material in small cysts formed at the site of the nodules and on one occasion a focal deposit of calcium salt. The fat cells are eventually replaced by scar tissue which usually contracts to form dimple-like depressions. In some cases the nodules have disappeared without trace of their former existence. Extensive atrophy of the subcutaneous fat has been described by Sundwall in a patient whose clinical course was compatible with relapsing febrile nodular non-suppurative panniculitis. Although Christian emphasized the absence of suppuration in the fat and break in continuity of the skin, Shaffer described a patient with liquefying features in a clinical course similar to that of Weber-Christian syndrome, except that the overlying skin became discolored and eventually became cyanotic, to form a bulla-like membrane, which subsequently broke down, and a sterile, yellow-brown fluid full of fat globules exuded. Bunnell and Levy reported a somewhat similar case. Ungar studied a patient thoroughly from the pathologic standpoint and found that the affected adipose tissue presented a variety of lesions. There were areas of 1) suppurative inflammation, 2) granuloma-like change, and 3) healed inflammation with residual changes. Bendel[12] likewise rated the histopathological changes as non-specific and varied in most cases. His description of the changes observed by himself and others may be taken as a good summary of the essential facts.

"The usual gross appearance is that of small subcutaneous nodules, usually on the thighs or legs at first, which may or may not be tender, which frequently show no disturbance of the overlying skin but may exhibit ecchymosis, and even occasional ulceration which are usually ill-defined and almost fluctuant. These may coalesce to form large nodules. On healing, there is usually a depressed area, which is permanent and corresponds in depth to the thickness of the panniculus. Microscopically, the epithelium as a rule, is little altered. The corium may show edema and increased vascularity. In early lesions, lipolytic histiocytes (macrophages), derived from the cells or reacting tissue, appear in the fat spaces and produce a foam-cell appearance by the injection of fine droplets of the fat, which appears to have been altered so that it behaves as a foreign body, calling forth a foreign body response. Between the fat spaces lymphocytic infiltration is seen. As time goes on, the foam cells regress and the nuclei tend to fuse, this development giving the cells the appearance of giant cells. As this activity is taking place,

the stroma becomes more densely infiltrated with lymphocytes and mononuclear cells, which obliterate the empty fat spaces in many places. An interesting early finding may be the swelling and thrombosis of the smaller blood vessels. The larger arterioles may show edema of the muscularis, with divided endothelial proliferation. Around the larger vessels definite lymphocytic infiltration is seen. The changes are seen early and persist in the older lesions. The last stage would appear to be fibrosis, with healing."

Ungar expressed disagreement with the classic description in part and said that histologically the initial lesion is distinguished by leukocytic stasis in the blood capillaries and focal suppurative inflammation in the adipose tissue (c.f. Lever). "These manifestations are followed by the development of granuloma-like lesions, which arrive on the axis of the fibrous substance; the process terminates in scar-like formations, or foci or foamy cell alteration. Shaffer stated that the last mentioned process results in liquefaction, as demonstrated by the loss of outline of the foam cells, with development of an amorphous foamy matrix in which the vesicular nuclei as well as the inflammatory round and polymorphonuclear cells are suspended." It is obvious from these descriptions that the pathologic picture of the Weber-Christian syndrome is not specific. In fact the same findings have been described following the injection of various agents including carcinogenic substances used in experimental research on hamsters. Similar changes have been observed after actual trauma, the injection of oily or other foreign substances, bacterial or non-bacterial, particularly insulin (Orr). It is essentially a foreign body reaction.

Clinical Manifestations. The typical clinical picture of the Weber-Christian syndrome is well known, and the summary of the features by Bendel in 1949 covers the essential facts. Subsequent reports have merely called attention to certain atypical cases. Bendel stated that "relapsing febrile nodular panniculitis or Weber-Christian disease, is characterized by recurring bouts of fever associated with the appearance of crops of subcutaneous nodules, varying from the size of a pea to several inches in diameter, usually on the thighs and arms, frequently on the abdomen, back and legs. These manifestations may remain separate or become, by confluence, indurated areas of subcutaneous fat. The nodules, which may be either painless or tender to touch, are frequently erythematous and raised above the surface of the normal skin. The pathologic changes appear to be necrosis of the subcutaneous fat, with infiltration by lipophages and eventually fibrosis. Over a period of months the nodules may slowly regress, leaving shallow or deep-pitted areas covered by normal skin. As a rule, no pathologic changes are observed in the other systems of the body, although death from the disease has been reported. In a few cases an enlarged spleen and leukopenia have been outstanding features.

The matter of laboratory findings in this process has already been covered, except that in his recent report Shuman noted a definite reduction in adrenal cortex function suggested by low 17-Ketosteroid excretion, positive reactions to the Robinson-Power-Kepler tests and absence of hyaluronidase inhibition on skin tests after epinephrine administration.

Certain pigmentary changes have been observed in recent cases. Gertler, for example, noted deeply pigmented lesions while Johnson and Plice[42], Machacek[55] and Samitz and Coletti[74] each reported an example of this disease in a colored person. Certain local changes in the lesions, such as focal

calcification in advanced lesions was reported by Bunnell and Levy. Atypical distribution of lesions, such as nodules on the hand and in the breast, have also been observed. One of 3 of the cases reported by Schwartz, Loftus *et al.* had extensive involvement of the adipose tissue with changes in the size of the heart and of the liver and spleen. Diabetes, as previously mentioned, has been observed in association with a number of cases, and the matter of the liquefaction has already been mentioned. Sanford and his group, thought that cryoglobulinemia may be of diagnostic importance in the Weber-Christian syndrome. This of course is of hypothetic interest.

With regard to fatalities, I have been able to collect 14 cases of Weber-Christian syndrome with a fatal termination. Bailey[8] was the first to describe a patient with relapsing febrile nodular non-suppurative panniculitis who apparently died of the disease, but Miller and Kritzler[56] were the first to report such a case with changes in the fat at a necropsy. This patient, a woman of 34, had no specific lesions, but there was gross involvement of the fat. Death was apparently due to prolonged cachexia, fat embolism and pneumonia. Tilden *et al.*[84] had previously recorded a patient who had died and the necropsy showed 18 months after study disseminated tuberculosis. There were no clinical signs of tuberculosis at the time of attack. Histologically, there was endothelial proliferation of the vessels, the arterial walls were edematous. Spain and Foley[81] reported a case in which death was apparently due to uremia and glomerulosclerosis. Ungar's[85] patient apparently died of peritonitis. Mostofi and Engleman's[60] patient, a Filipino man, showed fatty lesions of the subcutaneous, epicardial, peripancreatic, periadrenal and mesenteric fat. Jones, Lamb and Goldman's[43] patient was a 52-year-old white woman, whose necropsy showed apparent destruction of the normal architecture of the liver lobule due to fibrous bands which divided the liver cells into abnormal lobules which did not show central veins. This fibrous tissue was markedly infiltrated with mononuclear cells and in many places necrosis had set in. In some sections, this fatty degeneration was so pronounced that the tissue resembled fat. The spleen showed marked fibrosis and considerable congestion of the sinusoids. The skin showed findings resembling those recorded previously by Shaffer in his case of liquefying nodular panniculitis. Bjornstad's[15] patient died after 4 weeks in the hospital. The necropsy showed sclerosis and fatty degeneration of the liver and slighter sclerosis of the spleen. Friedman's[33] patient showed a considerable amount of suppuration and death was apparently due to staphylococcic septicemia. The necropsy showed a number of nodules on the intra-abdominal fat deposits. Hallahan and Klein's patient apparently died of "Hodgkin's Disease" of the fat. Shuman's fatal case of relapsing panniculitis was associated with widespread nodular involvement of the subcutaneous panniculus and high fever. Findings in the fat were somewhat reminiscent of Hodgkin's Disease, except that no Sternberg-Reed cells could be found. Shuman comments that the report of Hodgkin's Disease in 2 cases is an important fact which requires further scrutiny. One of the 2 patients studied by Hanrahan and colleagues died of the disease. Necropsy showed severe fatty metamorphosis of the liver, acute hyperplasia of the spleen and several areas of panniculitis. Sanford and coworkers' patient died 10 days after hospitalization, approximately 3 months after the onset of the illness. Unfortunately no necropsy was performed. The fatal case of painful

febrile suppurative nonfistulous panniculitis reported by Van der Meieren and DuBois-Mercier could not definitely be classified as Weber-Christian disease.

Diagnosis. Although Weber-Christian syndrome is usually relatively easily diagnosed, certain nodular processes, may be difficult to differentiate from it. Some of these processes are: 1) subcutaneous fat atrophy, 2) insulin lipodystrophy[51,44,25], 3) hypodermic injections and drug addicts, 4) trauma, 5) erythema nodosum, 6) erythema induratum, 7) sarcoid of Darier-Roussy, 8) dermatomyositis, 9) morphoea, 10) adiposis dolorosa, 11) subcutaneous fat necrosis in the newborn, 12) disseminated lupus erythematosus, 13) benign, nodular hypodermite; 14) thrombophlebitis 15) nodular syphilis, 16) leprosy, 17) nodular vasculitis[87,92,58], 18) spontaneous panniculitis of Rothmann and Makai, 19) metastatic neoplasm and lymphoma. Attention to the features of each of these processes, as well as a study of the material removed histologically, will lead to the correct diagnosis.

Treatment. Evaluation of any form of treatment on the Weber-Christian syndrome is colored by the fact that individual attacks may resolve spontaneously and recurrences are unpredictable. However, certain forms of therapy occasionally yield temporary beneficial effect. Among these treatments are those with a bacteriostatic effect such as the sulfonamides (Miller and Kritzler). While sulfanilamide, sulfadiazine, sulfathiazole and sulfamerazine have all been used with apparent benefit, they have also failed (inadequate dosage?). After sulfadiazine and sulfathiazole had failed, Arnold administered sulfapyridine to an active case of Weber-Christian syndrome. On 5 occasions, sulfapyridine was withheld and relapses followed in 24 hours with elevation of temperature, the return of symptoms, increased sedimentation rate and leukocytosis. On re-administration of treatment with 3.5 gm. of sulfapyridine per day, the patient's condition returned to normal. Koch, in 1951, found sulfapyridine to be helpful in one case, but its actual value was in doubt because spontaneous involution was not excluded. On the other hand, Bunnell and Levy raised the question, as to whether Weber-Christian syndrome is due to prolonged administration of sulfonamides. Recent reports, such as that of Muri[61], indicate the possibility that the combined use of penicillin and sulfadiazine may be of value. Penicillin alone has been administered in some cases with but little benefit. Occasionally, it may be of great value, as in the patient reported by Zee[93] whose nodules disappeared after the use of 20,000 units of penicillin intramuscularly every 3 hours for 15 days to a total of 2,360,000 units. Hanrahan *et al.*[38] used penicillin in 2 cases; one with rapid healing, the other a fatal case. In this latter patient there was also no effect from dihydro-streptomycin, aureomycin, antihistaminics and sulfonamides of various types. Penicillin was also advised by Schwartz, Loftus and Fishler as well as by Livingstone and by Kooij. Frost[34] used penicillin orally followed by 500 mg. of aureomycin (Lederle) every 6 hours orally for 48 hours with clearing up of the lesions, with a 3-months' follow-up without recurrence. However, the actual effect of the treatment was not definite. Rubin and Blanc used penicillin combined with streptomycin in 2 cases; they found improvement in one of the 2. Gay Prieto and his coworkers[35] used streptomycin, 1 gm. per day, with vitamin E (100 mg. per day) without much effect. The subsequent use of aureomycin followed by penicillin and 10 units of insulin per day

was likewise of no value. Brudno, as well as Kennedy and Murphy, have suggested the possible relationship of Weber-Christian syndrome to the group of collagen diseases. Drew, Wasson and Morris[28] administered ACTH with temporary recession of the lesions, but when the hormone was withdrawn there was an exacerbation. Shuman also employed cortisone in his patient with high expectation for success. The ameliorative effect of the hormone on granulomatous processes suggested that it would be beneficial in Weber-Christian syndrome. In 10 days of treatment, however, there was little effect until the eighth day, when the temperature returned to normal. There was no alteration in the size of the lesions. The temperature remained normal for 5 days and then returned to previous levels of 103° F. after the cessation of cortisone therapy. ACTH administered during the last few days prior to death, likewise showed no effect.

Numerous other procedures have been employed, with or without definitive results: the removal of bromide and iodide medication, the use of quinine, intravenous gentian violet, ferrous citrate, viosterol, antisyphilitic therapy, antimony, gold, arsenic and mercury, Roentgen-ray therapy, multiple blood transfusions, hormones, such as thyroid and pituitary extract and removal of foci of infection. The use of salicylates as well as some of the antihistaminic preparations have been advised, apparently again with equivocal results.

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PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF JANUARY 20, 1953

Darstine, 1-(3-hydroxy-5-methyl-4-phenylhexyl)-1-methyl piperidinium bromide, a visceral anticholinergic agent. E. C. McManus, V.M.D., PhD., J. M. Bochey and K. H. Beyer, M.D., Ph.D. (Research Division, Sharp & Dohme, Inc.). It has been the purpose of this study to develop a new potent anticholinergic agent which would possess a greater selectivity for the gastrointestinal tract than available effective agents. From a series of β-dialkylaminoethyl substituted benzyl carbinol quaternary salts, 1-(3-hydroxy-5-methyl-4-phenylhexyl)-1-methyl-piperidinium halide, Darstine, was selected for extensive laboratory and clinical study.

The anticholinergic potency of Darstine and the reference agent, methantheline, upon several visceral structures have been compared. The two agents, administered intravenously, were equipotent approximately in antagonizing the increase in tonus induced in the Thiry fistula preparation by a rapid intravenous injection of methacholine. When the inhibitors were administered orally, Darstine was more potent than methantheline and the inhibitory effect of the former compound was lost at less than one-half the rate for the latter drug. The activity of the two agents in antagonizing vagally stimulated gastric hydrochloric acid secretion in the acute total gastric pouch of the dog was comparable. The stimulant used was 5-ethyl-5-(1, 3-dimethyl-1-butenyl)-barbituric acid. A marked difference existed between the effect of the two agents in antagonizing methacholine stimulation of parotid secretion in the dog, Darstine being only about one-fourth as inhibitory as methantheline. An intravenous dose of Darstine, 2 to 4 times greater than of methantheline, was required to produce an equivalent cholinergic inhibitory effect on the urinary bladder muscle of the trained unanesthetized dog. Cholinergic inhibitory potency of Darstine on the cardiovascular system of the dog was approximately one-half that of methantheline.

Thus, Darstine possesses a greater selectivity for the gastrointestinal tract of the dog. Clinical studies are in progress to determine whether the greater selectivity applies also for the human.

A Comparison of Absorption Rates of Glucose in the Upper and Lower Human Small Intestine. Alvin J. Cummins, M.D., and Raine Jussila, M.D. (Gastro-Intestinal Section, Kinsey-Thomas Foundation, of the Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia). Data from animal experimentation comparing absorption rates in various levels of the small bowel are meager and conflicting. Similar data are not available for the human. Because of the significance of such knowledge in various clinical conditions such as partial intestinal resection or rapid passage of ingesta into the lower small bowel (as after gastric resection), it was considered worthwhile to attempt comparison studies of absorption rates in the human subject, using glucose as the test material.

The intubation technique described by Nicholson and Chornock was em-

ployed, which permits measurement of the absorption rate of a 45-cm. segment of the small bowel. In the present procedure the rate of absorption for 5% glucose in the upper intestine (duodenum and upper jejunum) was compared with that in the lower ileum in the same patient, the tests being run consecutively. Data so obtained were contrasted with those in which the same procedure was carried out with the tube remaining in the same area of the upper small bowel for both tests, to determine the reproducibility of results.

Analysis of the data obtained indicates that in 7 control experiments in which the segment studied was the same, the checks between 2 consecutively performed tests were gratifyingly close, the mean difference in absorption rate being 4%. In 5 patients in whom a comparison of rates in the upper and lower small bowel was made, the ileum showed a mean rate 26% below that in the upper intestine. The results also suggest that the absorption rate for water may be reduced in the ileum, as indicated by the larger volumes of fluid aspirated from that area. No difference in the concentration of unabsorbed glucose was observed in the aspirates from either site, demonstrating that reduction in absorption rate in the ileum is not due to greater dilution.

Lipolytic Activity of Human Blood Serum. Its Relation to Pancreatic Lipase-Inhibitors of Serum. PAUL GUTH, M.D., SIMON KOMAROV, M.D., PH.D., HARRY SHAY, M.D., AND CHARLOTTE ZISLIN, B.S. (Samuel S. Fels Research Institute, Temple University School of Medicine, Philadelphia, Pa.). Several phototurbidimetric procedures for lipase determination in canine pancreatic juice were developed, using natural fat ("Lipomul oral" vegetable oil emulsion) or tributyrin emulsion in either 0.15 ionic strength, pH 7.05 ± 0.05 phosphate buffer or 0.5% sodium barbital buffer. Incorporation of 0.004% potassium oleate and 3% gelatin resulted in a striking increase in the rate of reaction. Additional acceleration in the activity of pancreatic lipase resulted from incorporation of either 2% Merck sodium choleate or 0.75% sodium desoxycholate. With each procedure the reaction was zero order with respect to substrate concentration with total hydrolysis not over 60%. Rectilinear regressions of zero order constant on protein nitrogen of pancreatic juice were obtained with standard error of the estimate 4.15% over a 5 fold range and less than 10% over a 14 fold range (A. Grossberg-unpublished data). With our newest natural fat substrate in barbital buffer, it was possible to determine quantitatively protein nitrogen in pancreatic juice from a single reading in a Klett-Summerson colorimeter after 15 minutes incubation at 32° C. with S.D. of % error = 5.7 over the range of approximately 0.5 to 6.0 micrograms.

With these procedures, no lipolytic activity was observed in many specimens of normal and pathological sera, while activity was always detected after the addition of 0.1 to 0.02% pancreatic juice. Lipolytic activity was observed in blood sera in many cases of pancreatic disorders, the highest being equal to the activity of the protein of pancreatic juice containing 7 mcg. nitrogen.

When increasing amounts of normal serum were mixed with dilute pancreatic juice, lipolytic activity of the latter was progressively inhibited, the units of lipase inhibited being proportional to the logarithms of the amounts of serum used.

When tributyrin was substituted for natural fat in the substrate, the "tributyrinase" activity could be measured turbidmetrically in pancreatic juice and blood serum with or without

sodium desoxycholate. There was no correlation between the lipolytic activity and the tributyrinase activities measured with or without sodium desoxycholate in the substrate in various specimens of pancreatic secretion and blood sera.

The Use of Sodium Dehydrocholate in the Diagnosis of Biliary Tract Disease. A Preliminary Report. JOSEPH M. GAMBESCIA, M.D., CHARLES M. THOMPSON, M.D., ALEX ULIN, M.D., AND WILLIAM SHOEMAKER, M.D. (Departments of Gastroenterology and Surgery, Hahnemann Medical College and Hospital, Philadelphia, Pa.). Sodium dehydrocholate administered intravenously produces a measurable response in both normal and abnormal states. In this study, comparison of duodenal aspirates as to volume and icterus index for three 20-minute intervals before and after the intravenous injection of 10 cc. of 20% sodium dehydrocholate indicates that a difference in response occurs under the following situations. 1) The normal gallbladder 2) Cholecystolithiasis (with or without impaired Roentgen function) 3) Choledocholithiasis 4) Post-cholecystectomy.

This preliminary report entails the study of 7 normal and 52 abnormal situations and in essence supports the work of Lans, Stein and Meyer (Gastroenterology **18**, 1, 64).

The normal response comprises a fall in both volume and icterus index of the duodenal aspirate after the intravenous injection of sodium dehydrocholate apparently due to the diversion of the increased hepatic secretion into the gallbladder (reservoir function).

The abnormal response comprises a rise in volume and a decrease in icterus index following the intravenous administration of sodium dehydrocholate, a reflection of the inability of the gallbladder to accommodate the increased flow of hepatic secretion (no reservoir function) and an indication of the hydrocholoretic effect of sodium dehydrocholate (an increase output of secretion comparatively lower in pigment content).

Illustrative cases will be considered demonstrating the above mentioned categories.

Further study is necessary for proper definition of this test but at present, indications are that it will be of value in aiding to evaluate: a) the normal gallbladder; b) the abnormal gallbladder with normal concentrating function (cholecystography); c) post-cholecystectomy syndrome; and d) the jaundiced patient in whom it is not possible to visualize the gallbladder by Roentgen-ray and in whom the problem of biliary tract disease arises as a contributing cause to the jaundice.

BOOK REVIEWS AND NOTICES

LABORATORY TECHNIQUE IN BIOLOGY AND MEDICINE. By E. V. COWDRY, Washington University, St. Louis. 3rd ed. Pp. 382. Baltimore: William & Wilkins, 1952, Price, $4.00.

THIS fascinating book is an encyclopedia of investigative methods and laboratory techniques. It contains a little about most everything associated with the medical routine and research laboratories. In the past few decades, techniques have become so important, so numerous and so complex that a complete treatment would require a respectable library. This book is, in a sense, a catalogue to that library. Many of the simpler tests are given in sufficient detail to require no further reference. The purposes of the others are given and proper references cited. It goes even further by naming substances and then listing the tests and techniques by which they may be investigated. Authors, tests, techniques and substances are all presented alphabetically and may appear under various headings in various places so that one can find what is given about a subject in the shortest possible time. It may be only a lead but without this book the initial lead may be the hardest to locate. No laboratory man should be without this book within easy reach. E. A.

DE ANEURYSMATIBUS OPUS POSTHUMUM—GIOVANNI MARIA LANCISI, 1654-1720—Aneurysms The Latin Text of Rome, 1745. Revised, with Translation and Notes by WILMER CAVE WRIGHT, Emeritus Professor of Greek in Bryn Mawr College. (No. 10 in the Hist. of Med. Series of the N. Y. Acad. of Med.) Pp. 362; frontispiece of title page. New York: Macmillan, 1952. Price, $7.50.

THIS is a bilingual edition (Latin text on the left hand page, English on the right) of one of the chief works of the celebrated Italian anatomist, clinician and epidemiologist. The reader should remember that in the 18th century the word "aneurysm" was used to designate both any dilatation of a tube such as an artery (Grk: euruno) and one from which the blood bursts forth (Grk:euroein), that is, a ruptured aneurysm in the modern sense. With this in mind, he will better appreciate what the author has to say about the causes and production mechanism of cardiac as well as vascular aneurysm.

This translation of De Aneurysmatibus—the second part of Lancisi's "De motu cordis et aneurysmatibus" appears to be the only complete text in English, Erichsen's text in the Sydenham's Society's "Observations on Aneurysm" having omitted a large block of its Propositions as well as many other pages and words of the text. The first part, de Motu Cordis, has been omitted by Professor Wright, thus following the custom of modern writers. In fact, except for Crescimbeni's epitome of the double treatise, in which 17 pages were given to the first part, and only 6 to the second, the text of *de Motu* is apparently only to be found in the original Latin. For the present work, Dr. Wright has used Vol. 4 of the 1745 edition of Lancisi's Opera Omnia. She has also included her translation of Assalta's Life of Lancisi.

Dr. Wright, already well known for her annotated translations of Fracastorius' "de Contagione" and Ramazzini's "De morbis artificum", died in November 1951, while the text of this volume was in proof. E. K.

PROGRESS IN OPHTHALMOLOGY AND OTOLARYNGOLOGY. A QUADRENNIAL REVIEW. VOLUME I. PART I, OPHTHALMOLOGY. Edited by MEYER WIENER, M.D., and A. EDWARD MAUMENEE, M.D. PART II, OTOLARYNGOLOGY. Edited by PERCY E. IRELAND, M.D., and JOSEPH A. SULLIVAN, M.B. Pp. 666; 46 illustrations. New York: Grune & Stratton, 1952. Price, $15.00.

THIS compact volume provides a review of current concepts and recent advances in ophthalmology and otolaryngology by 72 contributors selected for thorough knowledge of their subject. The literature is reviewed from July 1946 to the present and a brief bibliography at the end of each chapter indicates the original source material. In a composite enterprise of this type, there are differences in viewpoint and in the quality of individual presentations but the topics are arranged in logical sequence and the subject material is dealt with critically. The major trends in current research and the changing concepts in medical and surgical treatment are adequately traced. Ophthalmologists and otolaryngologists will find this book informative, stimulating and useful. H. S.

A TEXTBOOK OF PHARMACOLOGY. By WILLIAM T. SALTER, M.D., Professor of Pharmacology, Yale University School of Medicine. Pp. 1240; 284 ills. Philadelphia: W. B. Saunders Co., 1952. Price, $15.00.

THIS excellent book brings a refreshing and highly personal approach to its subject, representing, as the author stated, his experiences and choices in the light of many hours spent at the bedside as well as long nights in the laboratory. The book reflects the dynamic personality of its most capable author. It is, therefore, a major loss to oncoming medical students and physicians that Doctor Salter died suddenly just before the preparation of this review. The basic facts of pharmacology are, of course, presented; but the mode of presentation, the numerous historical references, the unexpected but timely quotations, and the brilliant vivid style of writing make this more than just a recital of pharmacological facts. The book is warmly recommended to physicians and students. R. K.

POISONING. A GUIDE TO CLINICAL DIAGNOSIS AND TREATMENT. By W. F. VON OETTINGEN, M.D., National Institutes of Health. Pp. 524. New York: Paul B. Hoeber, Inc., 1952. Price, $10.00.

THIS book offers a very practical approach to the clinical problems of poisonings, as they occur in the experience of the general practitioner and the internist. The book is divided into four parts. The first deals with the classification of poisons, the medico-legal aspects and the emergency measures and equipment necessary for treatment. The second part deals with the problems of diagnosis and is very well done. Part 3 deals with management. The last section gives, in alphabetical order, 461 types of poisoning, their manifestations and treatment. The book should be most useful to all practicing physicians. R. K.

PRINCIPLES AND PRACTICE OF ANESTHESIOLOGY. By VINCENT J. COLLINS, M.D., Director of the Department of Anesthesiology at St. Vincent's Hospital of the City of New York. Pp. 528; and 99 ills. Philadelphia: Lea & Febiger, 1952. Price, $10.00.

THE author has done a very excellent piece of work in writing this textbook. Dr. Collins is to be congratulated on his presentation of the subject of anesthesiology. His presentation is well organized and the scope is broad.

This is the first textbook which has presented the entire subject of anesthesiology in such a complete fashion without getting the reader lost in vague theories and explanations of the basic physiological and pharmacological principles of anesthesia.

The six chapters which are devoted to the physiology of respiration, transportation of the physiologic gases and circulation are very well done. Anyone reading these chapters will receive a very excellent review of the basic principles of cardio-respiratory physiology.

The section on complication is most valuable and is very complete in its presentation not only of complications during the administration of anesthesia but also complications which may be present prior to surgery and anesthesia and in the post operative period. He also discusses complications due to a disturbance of the temperature regulating mechanism.

Medical students, residents in anesthesiology and anesthesiologists will be pleased with this book because it contains information which cannot be found in any other single volume. L. K.

BRAIN MECHANISMS IN CORONARY DISEASE. CAUSATION, TREATMENT AND PREVENTION. By N. E. ISCHLONDSKY, M.D. Pp. 171; 45 ills. London: Henry Kimpton, 1952. Price, 25 shillings.

THE author believes that the primary cause of coronary artery disease is a chronic collision of rhythms. By this, he means that the individual has an imperfectly trained inhibitory process so that he cannot react neuropsychiatrically to changing stimuli smoothly and without friction because the rhythm produced by these stimuli collide with the conditioned responses he has developed. Prevention of coronary disease, therefore, consists in training the sense of rhythm in children by physical exercise and music and treatment consists in the development of social courtesy. There is the usual loose interchangeable use of hypertension and coronary disease so common in those dealing with the "cerebral" aspects of these diseases.

The author repetitiously and irritatingly refers to the proof of this concept. Proof consists solely in a statistical analysis of the incidence of coronary disease in several nations and races.

The author states "subjective thinking is . . . a deception since it leads to explanations and assumptions that sound extremely interesting, highly plausible and most tempting, consistent in themselves yet deprived of any foundation." This criticism is particularly applicable to his own book because he writes well and persuasively. L. S.

NEW EDITIONS

American Pocket Medical Dictionary. 19th ed. Pp. 639. Philadelphia: W. B. Saunders Co., 1953. Price, $3.25 plain, $3.75 with thumb index.

THIS standard work, now in its 55th year, has won for itself a foremost place in American Medicine. The convenient format of this pocket edition makes it a particularly useful and convenient publication. No physician, medical student or physician's secretary should be without one. R. K.

Outlines of Internal Medicine. Edited by CECIL J. WATSON, M.D., Head, Department of Medicine, University of Minnesota. 7th ed. Pp. 700; illustrated. Dubuque, Iowa: Wm. C. Brown Co., 1952. Price, $13.00.

IT is a pleasure to welcome the 7th edition of this well-known work, particularly because of the fact that it now is bound in a single cloth volume rather than in five loose-leaf sections. There is adequate coverage to serve those who wish to use the text for review purposes.
R. K.

Clinical Laboratory Diagnosis. BY SAMUEL A. LEVINSON, M.D., PH.D., Prof. of Pathology, Univ. of Illinois, and ROBERT P. MACFATE, CH.E., M.S., PH.D., Chief, Bureau of Labs., Dept. of Health, City of Chicago. 4th ed. Pp. 1146; 221 ills., 10 in color. Philadelphia: Lea & Febiger, 1951. Price, $12.00.

THIS is one of few good textbooks devoted to clinical laboratory methods and their interpretation. In this, the fourth, edition numerous changes have been made. A great deal of new information has been added while much obsolete material has been deleted.

The newer nomenclature in hematology is included and the authors provide a table for comparison of the terms recommended by the Committee on Nomenclature with those employed by others. Despite its comprehensiveness, the subject matter is well organized and is presented with clarity.

A valuable feature is found at the beginning of each chapter, namely, the brief instructive introduction into the physiology, chemistry, and clinical pathology of the organ or function under discussion.

This enlarged edition provides a complete text on clinical laboratory methods which will be helpful to medical students, medical technicians, clinical pathologists, and practicing physicians. C. Z.

Bacterial and Mycotic Infections of Man. Edited by RENE DUBOS, PHD., The Rockefeller Institute for Medical Research. 2nd. ed. Pp. 886; 80 ills., 18 charts, 73 tables. Philadelphia: J. B. Lippincott Co., 1952. Price, $7.50.

SINCE its introduction in 1948 the first edition of this volume has become the standard reference book in medical bacteriology, immunology and mycology. The second edition is even better, partly because of the addition of new material on genetics, blood groups and chemotherapy, but more so because of revision of old material. All of the 37 contributors are authorities in their respective fields; thus, each chapter is in effect a reliable and cmprehensive treatise of the subject. Especially commendable is that on allergy by Chase and on mycology by Conant.

Although this volume is expressly intended to serve as a text for medical students, the average uninitiated reader will be overwhelmed and confused by the amount of detail presented. The beginner will not enjoy reading a collection of authoritative and often profound treatises among which there is little continuity. He will be annoyed by the numerous references in the body of the text. There are few photographs to provide visual concept. As a result the reviewer is not inclined to recommend this volume for the use of students who are being introduced to the study of infectious diseases.

On the other hand, it is definitely the best reference book in its field for interested practitioners, teachers, research workers and advanced students. The basic approach is entirely sound in that bacteriology is presented in terms of the host-parasite relationship of which infectious disease is simply one or more of the manifestations. And because there is continuous emphasis upon the application of fundamental information to clinical medicine, this volume should be available to all persons who are vitally concerned with the problems of infectious disease. Deserving of comment is the low price which was made possible through financial aid from the National Foundation for Infantile Paralysis. E. S.

Operating Room Technic. St. Mary's Hospital, Rochester, Minnesota. 4th ed. Pp. 345; 219 ills. Philadelphia: W. B. Saunders Co., 1952. Price, $6.50.

THIS book was written principally as a guide for the operating room nurse, and as such it is invaluable. The first chapter describes the operating suite at St. Mary's Hospital, which is a well planned unit. The remaining chapters are devoted to the description, in brief and almost abstract form, of the various surgical operations done in the large modern hospital. Necessary equipment is listed in reasonable detail. The book is quite up-to-date, photographs and illustrations are numerous and accurate, and the field of general surgery and allied subspecialties is well covered.

This book should be a must for the conscientious operating room supervisor and should be helpful in student nurse instruction. G. R.

Textbook of Physiology. BY WILLIAM D. ZOETHOUT, PH.D., AND W. W. TUTTLE, PH.D. Loyola University and State University of Iowa, College of Medicine. 11th ed. Pp. 692; 302 ills. St. Louis: C. V. Mosby, 1952. Price, $4.75.

THE eleventh edition of this valuable text has several chapters which have been completely revised. Much new material pertaining to respiration is presented. Energy and weight balance have been reorganized. Dynamic equilibrium of body constituents has been stressed. Progress in neurophysiology has been included. The illustrations continue to be good. The book covers the area between complete larger texts and very brief ones. Dental, pharmacy and normal school students should find it useful. M. O.